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ATHETOSIS

II. SURGICAL TREATMENT OF UNILATERAL ATHETOSIS

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In 1932 Buchanan and one of us (P. C. B.)[1] reported a case (case 1) of unilateral (left) athetosis with spastic hemiparesis and unilateral convulsive seizures involving the left side which appeared two weeks after an uncomplicated tonsillectomy in January 1930. Two encephalograms, one made in May and the other in October 1931, revealed no abnormality that was considered significant. In November 1931, almost two years after the onset, the patient was operated on. The right central region was exposed. Electrical stimulation of the precentral gyrus in its middle portion elicited "complex movements of the left arm identical with those involuntary athetoid movements previously observed in the patient." This portion of the precentral gyrus was then extirpated. Microscopic examination revealed that the portion of cortex removed consisted almost entirely of area 6 of Brodmann. When the patient was last seen, on Nov. 13, 1935, it was stated that since the extirpation, over four years previously, the athetoid movements had not recurred. The convulsive attacks had persisted but had diminished in frequency and severity. The continuous slow, sinuous involuntary movements present before operation had never recurred. She had continued to have attacks of groups of sudden paroxysmal seizures at intervals of about two weeks. These seizures were of momentary duration. The patient did not lose consciousness; the left arm and leg became rigid in extension, and she would fall if she was standing when they occurred. Several such attacks occurred at intervals of a few minutes. She was taking 90 mg. of phenobarbital three times a day. Examination revealed a typical hemiplegic gait. The left arm was carried flexed to a right angle at the elbow. No athetoid or involuntary

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1. Bucy, P. C., and Buchanan, D. N.: Athetosis, Brain **55**:479-492, 1932.

movements were present. The left arm could be raised above the head, flexed and extended at the elbow. Although movement of the left wrist and fingers was limited, the patient was able to grasp objects firmly; she had some difficulty, however, in relaxing her grasp. There seemed to be a trace of reflex forced grasping.

If one agrees with Wilson [2] that "If after development of tremor, chorea or athetosis a destructive lesion leads to cessation of the involuntary movement, then that lesion must be so situated as to interrupt the neural mechanism that has been producing the movement," one can only conclude, as we did in agreement with Wilson, that the involuntary movements of athetosis are protluced by impulses arising from the precentral region and passing over the efferent fiber tracts of this cortical motor mechanism. It is our belief, supported by the new cases to be presented, that area 6 and its independent motor projection system are the system primarily concerned in this phenomenon, rather than area 4, the Betz cells and the pyramidal tract, as stated by Wilson. However, it should be added that Wilson was fully cognizant of the fact that some motor mechanism other than the Betz cells and the pyramidal tract also must be concerned. He stated: "For the complex movements of chorea (or athetosis [3]), to take an example, we must postulate a motor center higher in a physiological sense than that of the motor region *sensu strictori* (area 4 [3]) and both clinical, pathological and experimental evidence suggests that *such a centre lies in front of the rolandic area.*" [4] It is obvious that our opinion, that the impulses giving rise to these involuntary movements must arise from area 6, is substantially in agreement with that of Wilson. Our only disagreement lies in the fact that he apparently believed the impulse to be transmitted thence to area 4 and to descend to spinal levels by way of the pyramidal tract. We, on the other hand, believe them to be transmitted by descending (nonpyramidal) fibers which pass directly from area 6 and to a less extent from area 4 to subcortical centers and thence by a second (or third or fourth) neuron to spinal centers, for reasons which will be stated in the discussion of case 2. Support is also to be found in Jakob's [5] case 18, cited by Wilson.[2] Briefly, in Jakob's patient suffering from severe athetosis, hemiplegia developed. With the onset of the paralysis the athetosis vanished, *never* to return during the remaining eighteen months of the patient's life. On the other hand, the hemiplegia lasted but a few days and then largely disappeared. It seems

2. Wilson, S. A. K.: Disorders of Motility and of Muscle Tone, Lancet **2**:1-10, 53-62, 169-178, 215-219 and 268-276, 1925.

3. Our insertion.

4. The italics are ours.

5. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923.

most likely that the temporary hemiplegia was the result of a temporary interruption of the activity of the pyramidal tract. However, it is unlikely that the impulses responsible for the involuntary movements were transmitted by this pathway, else they would have returned with its recovery. It is far more likely that some other system of fibers lying in close proximity to the pyramidal tract was responsible for these movements and that these fibers were more severely and permanently damaged than the fibers of the pyramidal tract. Such a fiber system is the parapyramidal system,[18] the nonpyramidal efferent projection fibers of areas 4 and 6.[6]

Although the results obtained in the original case were more or less accidental and unanticipated, they naturally led to a search for other suitable cases in which this surgical procedure could be applied and in which the phenomenon of athetosis—of spontaneous involuntary movements—could be more extensively studied. Two such cases are here reported and discussed. In the first case the involvement was by far the more severe and supplied the most information.

CASE 2.—*Right spastic hemiparesis and generalized involuntary movements, worse in right upper extremity, present from birth. Large amount of barbiturates abolished involuntary movement, impaired fine coordinated voluntary movements and left gross voluntary movements intact. Extirpation of "arm" area of left area 6 abolished involuntary movements in right upper extremity. This was confirmed by electromyographic tracings. Conclusion: Involuntary movements arose predominantly from abnormal activity of area 6.*

R. E. W. was first seen in the outpatient department of the University of Chicago Clinics on Aug. 25, 1930, but he was not admitted to the hospital for careful study until Jan. 19, 1935, at which time his condition did not seem to have changed from that presented in 1930. He was born on Oct. 31, 1912, the first child in a family of three children. Parturition, at full term, was of nine hours' duration and is said to have been "difficult," although no instrument or anesthetic was used. The child was cyanotic at birth and remained so for from one to one and one-half hours. His survival was despaired of by the attending physician, who found it necessary to concentrate attention on the mother because of her precarious condition. The grandmother finally revived the infant by breathing into his mouth.

The immediate family consisted of the mother, aged 44, and the father, aged 43, both of whom were well except for infections of the paranasal sinuses, and a brother, aged 17, and a sister, aged 18, who were both well. No similar or other neurologic illnesses within the family were recalled. So far as is known, all the members of the family were right handed.

The patient was said to have been tongue-tied at birth, and the tongue was "cut" when he was 3 weeks old. He suffered from whooping cough, measles, chickenpox and mumps during childhood. The illnesses were in no way unusual and apparently were not accompanied with complications. He had "influenza" in 1919. His tonsils and adenoids were removed in 1926, and several tenotomies were performed on the lower extremities in that year.

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6. Levin, P. M.: The Efferent Fibers of the Frontal Lobe of the Monkey, Macaca Mulatta, J. Comp. Neurol. **63**:369-419, 1936.

The parents had always noted that the patient did not use his right arm. During early infancy he always picked up toys and other objects with the left hand. When he was 6 months of age his head began to be drawn to the right, and at 8 months involuntary movement of the right upper extremity first appeared. These movements grew progressively worse until he was about 16 or 17 years of age. After that they continued unchanged. The greatest progression, however, occurred before he was 10. When he was 9 years old the involuntary movements in the fingers of the right hand became so severe that in order to prevent ulceration it was necessary to bind them together. After that he constantly wore a cotton glove on his right hand, the fingers being bound tightly together by adhesive tape. He would wear out from three to four such gloves each week.

As the movements increased in severity they extended to other parts of the body, until finally the face and all four extremities were involved. It was not known when the movements first appeared on the left side, where they were always much less severe than on the right. The right arm was always the member most severely involved. The involuntary movements were always mild in the lower extremities.

It was noted that the involuntary movements were absent during sleep; and although almost constantly present during waking hours, they were altered by various circumstances. Rest and relaxation as well as concentration of attention on something else definitely decreased their activity. Excitement, talking or other motor activity greatly increased the severity of the involuntary movements.

The patient was able to hold up his head at 1 year of age and by the age of 2 was able to talk, although he always suffered from considerable dysarthria. The parents did not recall when he was first able to sit up unaided. He had never been able to walk or stand unsupported.

When he was from 4 to 6 years old the parents noted that his right arm was becoming stiff and somewhat later that the same condition was developing in the right leg. The arm gradually became flexed at the elbow and drawn up against the chest. The lower extremities became flexed at the knees and hips and strongly adducted. In 1926 several tenotomies were performed, which served to straighten the lower extremities.

For several years before he was seen at the clinics he had traveled about in a three-wheeled cart, propelled by his feet and guided by his left hand. He was able to travel from 8 to 10 miles (13 to 16 kilometers) at a time in this device.

He proved to be intelligent and had studied diligently with the aid of a tutor. He had completed the grade school and high school studies and at the time he entered the hospital was engaged in studying collegiate subjects, such as literature, languages, etc. The patient used the left upper extremity for writing, typewriting and drawing; at drawing he was amazingly proficient. The right upper extremity was useless and because of almost constant severe involuntary movements was the source of great concern to the patient. He definitely felt that the involuntary movements were the cause of his greatest discomfort and disability. He had seriously considered having the right upper extremity amputated in order to obtain relief. The lower extremities were weak, and he experienced great difficulty in their coordinated control, but they were sufficiently useful to propel the cart in which he rode for long distances.

Physical and Neurologic Examination.—The patient was alert, intelligent and cooperative. He was able to sit up in bed or in a chair without difficulty. He could not stand unaided.

Speech: The patient spoke rather slowly and with severe dysarthria. The speech was thick, poorly articulated and jerky. The difficulty seemed to be a mixture of two phenomena: one, an impairment of the voluntary control of the mechanism of speech; the other, the constant interruption of the flow of speech by frequent involuntary movements of the larynx, tongue and face.

Involuntary Movements: These were noted throughout the skeletal musculature. They were much the most severe in the right arm and least marked in the legs. They were aggravated by attention to them, excitement and attempted voluntary movements, especially of the right arm. They were decreased or abolished by sleep, anesthesia, rest or concentration of attention elsewhere. They could be temporarily reduced by voluntary effort.

The involuntary movements of the face were not severe and were most noticeable about the eyes, particularly the right eye, which often closed involuntarily; this was particularly noticeable during attempted voluntary movement of the right arm.

During most of the patient's waking hours the head was definitely retracted. During severe involuntary movements elsewhere it was so strongly retracted as to make the larynx and neighboring structures prominent. The sternocleidomastoid muscles appeared to be markedly hypertrophied.

The head of the right humerus was dislocated anteriorly out of the glenoid cavity, this observation being confirmed by roentgenography. The right elbow was flexed to a fairly acute angle, and complete extension was impossible because of fibrous ankylosis. The wrist was slightly flexed, and the fingers, which constantly moved, were more or less extended. The involuntary movements at the shoulder joint were rotary, causing the hand and arm to describe a circle about 8 inches (20 cm.) in diameter. The movement at the elbow was violent and consisted of alternating flexion and extension. The movements of the hand and wrist were not so stereotyped. They were constant and of such severity as to require protection of one finger from another, as previously described.

The left arm also was frequently held flexed at the elbow, but it could be more readily extended, either actively or passively, than the right. The fingers were slightly flexed at the terminal phalangeal joints and were extended at the metacarpophalangeal joints. The movements of the left upper extremity were similar to those on the right but much less severe. The movements in general were athetoid, in that they were purposeless; they consisted of both rapid and slow components, at times were violent and were involuntary.

Involuntary movements in the lower extremities were more definite on the right side but much milder and less extensive than in the upper extremities.

Voluntary Movement and Muscular Development: Reference has already been made to the speech. Movements of the head and neck were possible but were slow and difficult and often impeded by involuntary movements.

The right extremities were somewhat smaller and shorter than the left extremities. Voluntary movement to a limited degree was present at the shoulder and elbow; at the elbow only slight flexion and extension were possible. The patient was unable voluntarily to produce any movement in the right wrist or fingers and could exercise little, if any, inhibitory control over the involuntary movements in them. Movements of the right lower extremity, although decidedly more extensive than in the right upper extremity, were still limited, slow and difficult. The movements were also awkward and uncertain.

The left extremities were much better developed than those on the right. Their movements were much more extensive, better coordinated, more rapid and freer. As previously stated, the patient was able to write and draw with the left hand,

although the influence of the constant involuntary movements was plainly seen in his writing (fig. 1 *A*). The left lower extremity was the most nearly normal of the four extremities. It could be moved accurately and extensively and was sufficiently strong to bear the weight of the body. Standing unaided was prevented because the right leg would suddenly draw up into a flexed, internally rotated and adducted position and perform a variety of slow, purposeless irregular movements during endeavors at standing or walking.

Reflexes: Perhaps because of the rigidity and constant activity, no tendon reflexes were obtainable in the right upper extremity. The radial, biceps and triceps jerks were judged to be of relatively normal intensity on the left. All the abdominal reflexes were present. The knee and ankle jerks were somewhat hyperactive and about equal on the two sides. The plantar reflex was flexor on the left and extensor (Babinski sign) on the right.

Other Examinations: Neurologic examination otherwise revealed a diminution of the visual acuity of both eyes due to refractive errors. The pupils, media and fundi were normal. The visual fields were full. Ocular movements were normal, as were the pupils and their reactions. Sensation over the face was intact. There was definite weakness over the right lower portion of the face. The function of the remaining cranial nerves was normal, except for the difficulty in speech and the involuntary movements noted. There were no sensory disturbances.

General physical examination of the chest and abdomen revealed no abnormal findings. The arterial pressure was 130 systolic and 85 diastolic and the same on the two sides.

Laboratory Examinations.—The Wassermann and Kahn tests of the blood and the Wassermann test of the cerebrospinal fluid were negative. Blood counts and urinalysis revealed no abnormality.

An encephalogram was made on January 22, 160 cc. of cerebrospinal fluid being removed and replaced by air. There was a somewhat greater amount of air in the entire subarachnoid space than is usually seen. No other abnormalities were present, the degree of deviation from the normal being surprisingly slight.

Summary of History and Clinical Findings.—The record is that of a man, 22½ years of age, who was born at full term after a prolonged and difficult labor. Marked difficulty in resuscitation occurred, and for from one to one and a half hours the infant was severely asphyxiated. Shortly after birth paresis of the right side of the body, which had been present since then, was observed. Involuntary movements, involving first the head and neck, appeared when he was 6 months of age. They rapidly progressed to involve the right upper extremity. They increased in extent and severity for several years, until finally practically the entire body was involved, the movements always being most violent in the right upper extremity. For several years prior to the patient's admission to the hospital the condition had apparently not changed.

Examination revealed typical right spastic hemiparesis and severe constant involuntary movements of the face, neck and extremities, most severe in the right upper extremity. These were abolished by sleep and anesthesia, lessened by rest and diversion of attention from them and aggravated by excitement, voluntary effort and concentration of

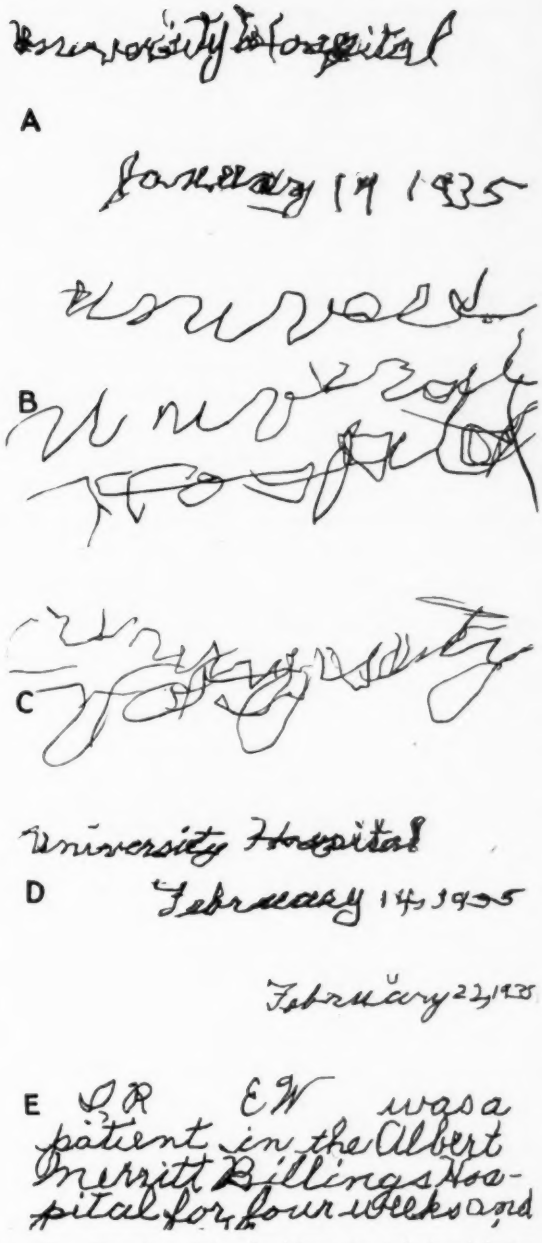

Fig. 1 (case 2).—Samples of handwriting, the left hand being used: *A*, on Jan. 17, 1935, before operation; *B*, on January 23, twenty-four hours after the administration of a large dose of barbiturates. The writing reveals no evidence of the involuntary movements, as shown in the preceding sample, but is coarse and illegible. *C*, same as *B*; *D*, on February 14, sixteen days after operation. The writing is more legible than any of the preceding samples. There is definite irregularity, but it is less marked than in the preoperative sample. *E*, on February 22, twenty-four days after operation.

attention on the movements. No sensory disturbances were present. An encephalogram was essentially normal, and the patient's general health appeared to be good.

Diagnosis.—It seems reasonable to suppose that the condition which this patient presented was the result of the disorder observed at and probably caused by birth. Whether the damage to the nervous system was produced directly by the trauma of birth or by the anoxemia which resulted from the prolonged period of asphyxia cannot be determined.[7] There was no evidence from the history or the clinical examination, nor was it possible to elicit any, as to the nature and location of the pathologic process within the nervous system responsible for the athetosis. The progression of the disorder for so many years raises interesting questions as to the nature of the pathologic process. However, it must be recognized that this progression is more probably explicable on the basis of progressive development of the nervous system than on that of a progression of the pathologic lesion.

It is clear that the patient was suffering from right spastic hemiparesis and severe involuntary movements, which we have interpreted as athetosis.

Effects of Barbiturates.—On January 22 at 11 a. m. in preparation for an encephalogram the patient was given 7½ grains (0.45 Gm.) of pentobarbital sodium (sodium ethyl [1-methylbutyl] barbiturate) by mouth; as that did not produce the desired anesthesia, 2 grains (0.12 Gm.) of soluble phenobarbital U. S. P. (sodium phenobarbital) was administered hypodermically. As soon as the patient fell asleep all involuntary movements stopped, and the resistance to passive movement which had previously existed in the extremities disappeared, except for the limitation of complete extension of the elbows, chiefly the right, which was due to contractures within the flexor muscles and possibly fibrous changes about the joints.

After the encephalogram was completed, at 12:06 p. m., the patient remained unconscious for some time, even the reaction of the pupils to light being absent. At 4:30 p. m. the pupils first reacted to light. At 5 p. m. the patient yawned, and at 6 p. m. he turned on his side. By 9:30 p. m. he had recovered consciousness sufficiently to talk and respond to questions, but he was still drowsy. *No involuntary movements were present.* He slept well that night, and when seen the following morning he was much brighter, and was able to converse at length intelligently. He stated that he was still somewhat tired and sleepy. No involuntary movements were present except under intense excitement or effort, when a few slight isolated movements could be seen in the right upper extremity. However, the patient was able to perform all voluntary movements that were possible before

7. Recent studies in our laboratory (to be reported on later by Dr. Leon Ectors) of the brain of an adult human being damaged by prolonged ischemia revealed that the most marked changes were disintegration of the ganglion cells of the cerebral cortex, particularly in the anterior and posterior central gyri, and of the Purkinje cells of the cerebellum. The basal ganglia and brain stem showed no significant changes.

the administration of the barbiturates. In fact, they were performed somewhat more easily, in that the involuntary movements were no longer present to interfere. There was, however, no reduction in spasticity, i. e., resistance to passive movement, nor was it observed to be increased. Although voluntary movements were in the main present as before, it was seen on close inspection that they were grosser, coarser and less well coordinated than before. This was particularly shown in the writing (fig. 1 *B* and *C*). Previously the writing, though greatly influenced and distorted by the involuntary movements, was clearly legible. Now, although devoid of the evidence of involuntary movements, it was large and coarse, and the letters were poorly formed and illegible. In other words, the barbiturates had abolished the involuntary movements and at the same time seriously interfered with the finer, well coordinated voluntary movements. For the remainder of that day the condition remained unchanged. When the patient awakened the next morning, about forty-four hours after the administration of the barbiturates, the involuntary movements had returned, although they were not as severe as previously. Little difference could be seen in the right upper extremity as compared with its former state, but there was still no involuntary movement of the left upper extremity, except for some more or less rhythmic movement of the thumb.

Comment.—It has been repeatedly demonstrated in experiments performed on monkeys that the various barbiturate anesthetics exercise a differential effect on the motor and premotor areas (Brodmann's areas 4 and 6, respectively) of the frontal lobe. Whereas under anesthesia produced by one of these drugs area 4 is highly and characteristically excitable, the excitability of area 6 is greatly reduced or often completely suppressed.[8] It is apparent, therefore, that the barbiturates depress either the premotor cortex (area 6) and its projection system (the parapyramidal fibers) or the subcortical centers which transmit the impulses from area 6 to a much greater extent than they depress the pyramidal system and its related cortex, area 4. This is important in consideration of the present case. It will be recalled that when the patient recovered consciousness, several hours after the administration of pentobarbital and phenobarbital, voluntary movements were present, but the finer coordinated movements, such as writing, were grossly impaired. This is exactly what would be anticipated from the experiments on infrahuman primates. As Fulton[9] stated: "Animals trained to perform skilled movements suffer impairment of the capacity to execute delicately adjusted maneuvers after the premotor area has been destroyed (area 4 remaining intact). Gross power is not, however, impaired." It may therefore be reasonably assumed that in this case the function of area 6 had been partially suppressed while that of area 4 and that of the pyramidal tract remained intact. If this view is accepted, the temporary absence of the involuntary movements becomes suggestive

8. Bucy, P. C.: Electrical Excitability and Cyto-Architecture of the Premotor Cortex in Monkeys, Arch. Neurol. & Psychiat. **30**:1205-1224 (Dec.) 1933.

9. Fulton, J. F.: Forced Grasping and Groping in Relation to the Syndrome of the Premotor Area, Arch. Neurol. & Psychiat. **31**:221-235 (Feb.) 1934.

as regards the genesis of such movements. From entirely different evidence [1] it has been previously concluded that the involuntary movements of athetosis arise as a result of abnormal activity of area 6. The presence of voluntary movements while involuntary movements were absent is also further evidence that the impulses giving rise to these involuntary movements are not transmitted by the pyramidal tract.

It should be pointed out that the evidence does not indicate a complete abolition of the functions of area 6 by the barbiturate anesthesia. Although the positive effects of area 6 were removed, the negative effects, i. e., inhibition, were apparently not disturbed. Thus, forced grasping was not present (nor was it ever observed in this case), and no definite increase in spasticity was demonstrable. It is probable that the barbiturates exercise a selective action on the various functions of area 6.

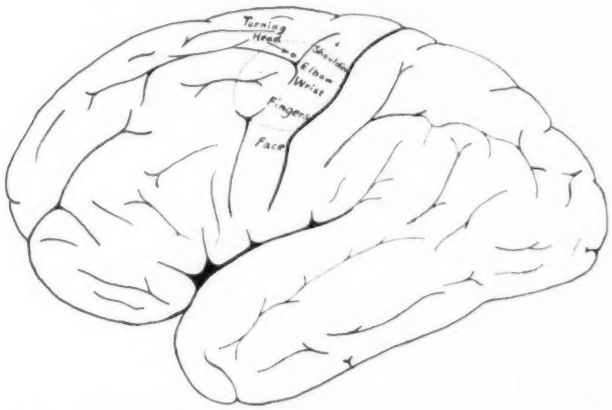

Fig. 2 (case 2).—Diagrammatic summary of the results of stimulation of the precentral region. The area enclosed by the dotted line was extirpated.

Stimulation and Extirpation of "Arm" Area.—On January 29, with the patient under ether anesthesia, an osteoplastic flap was reflected on the left side so as to expose the central area except its most medial portion. A drawing was made of the configuration of the exposed cortex, and on it were recorded the results of stimulation. These effects have been summarized, and the localization of the representation of the various portions of the body is recorded in figure 2. Grossly, the meninges and cerebral cortex appeared to be entirely normal. The entire exposed cortex was stimulated with a faradic current, a unipolar electrode being used. The representation of the shoulder, elbow, wrist, fingers and right side of the face was determined. From the posterior part of the first frontal convolution rotation of the head to the right could be elicited. No movements were produced in the lower extremities as the related portion of the brain was not exposed. The type of movement produced was similar to that elicitable from a normal brain. The involuntary movements from which the patient suffered were not duplicated by electrical stimulation. It was interesting that although voluntary movements of the right wrist and fingers had been completely absent, it was possible to produce

movement of the wrist and fingers separately or simultaneously by stimulation of the cortex. The stimuli were for the most part applied to the premotor area, i. e., area 6 of Brodmann, but no detailed effort was made to distinguish between the responses of area 4 and area 6 to stimulation.

After the representation of the right upper extremity had been mapped out, the area was circumscribed by the Bovie high frequency coagulation current, and a cone of tissue measuring 2 by 1.5 cm. at its surface was removed. The extirpation extended down into the lateral ventricle. The "face" area was intentionally spared, as was the anterior wall of the rolandic fissure. The area of extirpation is indicated on figure 2.

Postoperative Course.—At 3 p. m. on the day of operation, when the patient was arousing from the anesthesia, he was asked how he felt, and he replied, "All right." He was able to move the left arm and leg. No note was made as to involuntary movements.

At 5 p. m. the involuntary movements were absent from the right side but were present in the left arm and left side of the face, though not as marked as before operation.

There was no apparent increased difficulty with speech. Voluntary movements in the left extremities were as before the operation. Voluntary movement was possible in the right side of the face, but there was some weakness of the lower portion of the face, possibly greater than before the operation. The right arm and leg could not be moved. They were completely flaccid, and there was no limitation of motion except that due to fibrous ankylosis at the elbow.

First Postoperative Day (January 30): Involuntary movements were present in the left side of the face and left upper extremity as before operation. There were slight involuntary twitchings of the right eyelids, but otherwise no involuntary movements were present on the right side. Speech was very slow and poorly articulated. It was obvious that the patient knew what he wished to say but was practically unable to say it. There was no difficulty in comprehension. The right arm was completely paralyzed, and there was a definite increase in the resistance to passive movement, not quite as marked as before operation. The tendon reflexes were hyperactive. The right lower extremity was completely paralyzed, except for slight voluntary movement of the toes. The spasticity in the leg was comparable to that present before the operation. The knee jerk was definitely hyperactive, and the plantar response was extensor. Voluntary movements were present in the left extremities, and there was no alteration in the resistance to passive movement. However, purposeful utilization of the left upper extremity was definitely impaired; the patient could do little with it, and he was unable to write or even feed himself. The abdominal reflexes were active and equal. The head was drawn to the left.

Fifth Postoperative Day (February 3): The difficulty with speech was still present. The patient was able to say "All right" and a few other words with considerable effort and difficulty. There was no difficulty in the perception of written or spoken words and sentences. There were no involuntary movements on the right side except about the eye. The right arm was held semiflexed. Voluntary movements on the right side were limited to the face and to a few feeble movements in the lower extremity. Involuntary movements continued unchanged on the left side of the body. Although movement could be voluntarily produced in the left extremities, it was jerky, halting and grossly inaccurate. It was next to impossible for the patient to reach a definite goal by his voluntary efforts. The tendon reflexes were hyperactive in the right upper extremity but difficult to determine in the left because of the involuntary movement. The abdom-

inal reflexes were unchanged. The knee jerks were hyperactive and approximately equal. The plantar response was extensor on the right and flexor on the left.

Sixth Postoperative Day (February 4): The condition was unchanged except for the appearance of rapid, rhythmic flexion and extension of the right thumb. The patient was up in a chair for a short time.

Seventh Postoperative Day (February 5): There was definite improvement in the use of the left upper extremity; he used it in eating an apple.

Eighth Postoperative Day (February 6): There was definite improvement in the speech. Occasional slight involuntary flexion of the right middle finger occurred.

Ninth Postoperative Day (February 7): The patient thought that the left arm was as useful as before operation. Weak voluntary flexion was present in the right elbow. The patient was able to raise the right foot a few inches off the bed.

Sixteenth Postoperative Day (February 14): There were slight involuntary movements of the right fingers, principally the thumb and forefinger. They were, however, much less severe than before operation and did not require bandaging of the hand as previously. The movements were rhythmic, of a "pill-rolling," parkinsonian type. The incomplete weakness of the right lower portion of the face was present as before operation. The patient was unable to close the right eyelids without simultaneously closing the left, although those on the left could be closed independently. The tongue when protruded deviated slightly to the right. Except for slight movement at the elbow, no voluntary movements were present in the right upper extremity. Voluntary movement in the left upper extremity was as good as before operation, and the patient insisted that he could use the arm with more facility, especially in writing (fig. 1 *D*), he thought largely because of the absence of the constant jerking of his body by the involuntary movements of the right arm.

The patient had observed that on stretching after awakening the right upper extremity took part in the movement, although he was unable to reproduce the movement volitionally. The tendon reflexes were unchanged since February 3.

Eighteenth Postoperative Day (February 16): There had been no change in the involuntary movements in the preceding ten days, and the condition otherwise was practically as noted on February 14. The patient was discharged to his home.

Subsequent Course.—After leaving the hospital the patient wrote letters frequently. He stated that the involuntary movements had not returned to the right upper extremity to any greater degree than they were present at the time of discharge; i. e., they were limited to the fingers, involving primarily the thumb and forefinger. However, writing with the left hand had improved, as is shown in the accompanying specimen (fig. 1 *E*). By March he had recovered sufficient use of the right arm to help in guiding his cart, the first time in his life that the right upper extremity had ever proved useful. It is interesting in this regard that although forced or reflex grasping was never elicited during the patient's stay in the hospital, he reported in his letter of March 13 that whereas he could grasp objects with his right hand with little difficulty, it was difficult to release that grasp. At that time the patient noted also that the right leg was not "as nimble as it was before," though it was slowly improving.

On April 28 he reported that he was able to use the right hand alone to guide his cart and that the difficulty in relaxing the grasp of that hand was fast disappearing. He stated: "I have regained full control of my legs and can propel my cart as good as before."

The patient was seen in the outpatient department on July 5, a little over five months after the operation. Speech was much more clearly articulated than before the operation, and he was able to control his head and neck better and to hold them in a normal position. When he was not excited or talking there was little involuntary movement in the right upper extremity. When present, the movement of the upper arm was slight and consisted of a rhythmic internal and external rotation. There was no involuntary movement at the elbow. Movements of the fingers were confined largely to the thumb and forefinger and were present to a moderate degree as compared with the preoperative state. There were few involuntary movements of the face. There were slight and only occasional movements of the left hand. The patient was able to walk a little with assistance.

Subsequent letters indicated little additional change, except that the movement of the thumb and fingers seemed to diminish further. As he stated in a letter of October 23, "My fingers have ceased to interfere with each other almost entirely, the thumb especially."

The patient was last seen on May 4, 1936. There had been little change in his condition during the preceding year.

Blood Pressure and Cutaneous Temperature: The blood pressure was measured in both brachial arteries immediately after the operation, and the observations were continued at frequent intervals for five days. The differences in the pressures in the two arms was minimal, rarely being as much as 10 mm. of mercury. The difference was also inconstant, at times the pressure in the right arm and at other times that in the left being the higher.

No differences in the temperature of the skin were observed, although accurate measurements were not made after the operation. Prior to the operation careful measurements with an electrothermocouple revealed no essential differences in the two sides.

Electromyographic Records.—These were made for all four extremities both before and after operation. The method of making them was to lead off from two pads moistened with a solution of sodium chloride which were attached to the extremity to be examined. The input from these leads was suitably amplified and conducted to a rocking armature oscillograph devised in this laboratory (by T. J. C.). The sensitivity of the oscillograph was 1 cm. deflection for 1.5 or 0.3 millivolts, as indicated.

Before Operation: With the extremities as nearly at rest as possible, there was evident marked involuntary muscular activity, as shown by the action currents, in the upper portion of the right arm and the forearm, especially the latter (figs. 3*A* and 4*A*). Similar involuntary activity was recorded from the left forearm (fig. 5*A*), but it was definitely less intense than that in the right. Any voluntary movement caused a marked increase in the amount of electrical activity. In the right leg, below the knee, there was a little activity with the extremity "at rest." Here, too, voluntary effort greatly increased the electrical response. In the left leg there was no spontaneous activity recorded, but voluntary movements caused a burst of electrical activity.

In recording action currents from the right forearm it was noted that such general activities as talking increased somewhat the amount of spontaneous electrical activity obtained from the musculature of the arm.

After the Operation: On the eleventh postoperative day (February 9) records for the upper portion of the right arm and the right forearm gave evidence of no spontaneous muscular movements (figs. 3*B* and 4*B*). During attempts at voluntary movement, which gave but minimal movements, slight electrical activity appeared in the upper portion of the arm and almost none in the forearm. The upper portion

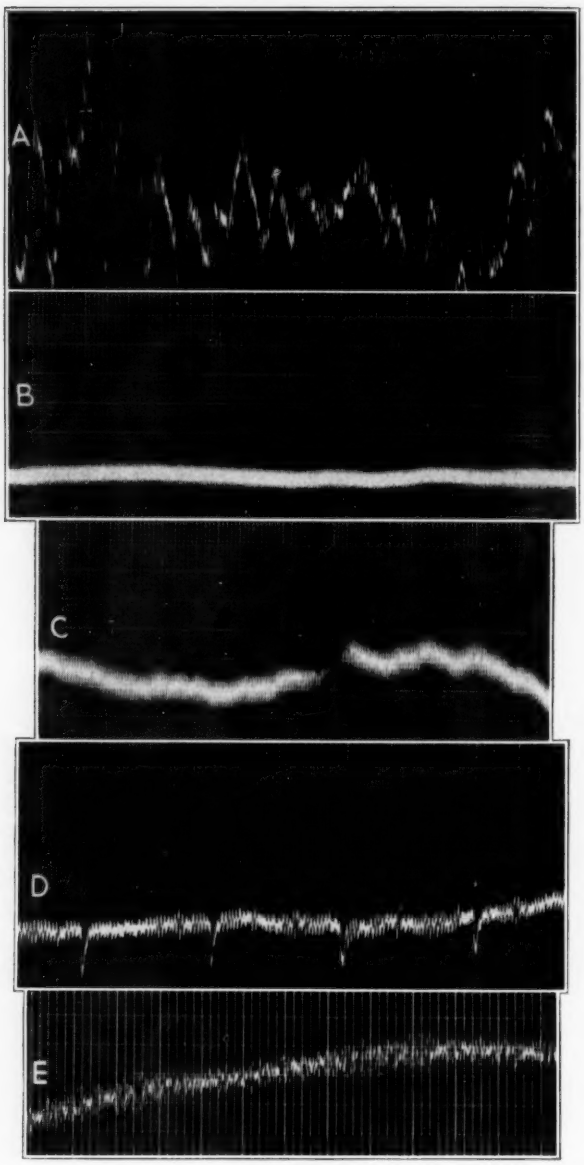

Fig. 3 (case 2).—Electromyographic tracings from the right forearm: *A*, on Jan. 28, 1935, before operation; *B*, on February 9, eleven days after operation; *C*, on February 15, seventeen days after operation; *D*, on July 5, five months after operation, and, *E*, on May 4, fifteen months after operation. The speed of the film was the same in *A*, *B* and C. It is shown by the vertical lines at the top of the tracing, the smaller intervals being one twenty fifth and the larger one fifth of a second. In *D* and *E* the film moved twice as fast. The sensitivity of the oscillograph was 1 cm. of deflection for each 1.5 millivolts in the first tracing. In the last four (*B* to *E*) the sensitivity was increased, and 0.3 millivolt caused 1 cm. of deflection. Tracings *B* to *D* show a 60 cycle fluctuation due to extraneous influences. In *D* a slower rhythmic fluctuation due to cardiac activity is seen. Figures 3 to 6 have been reduced to two-thirds the original size.

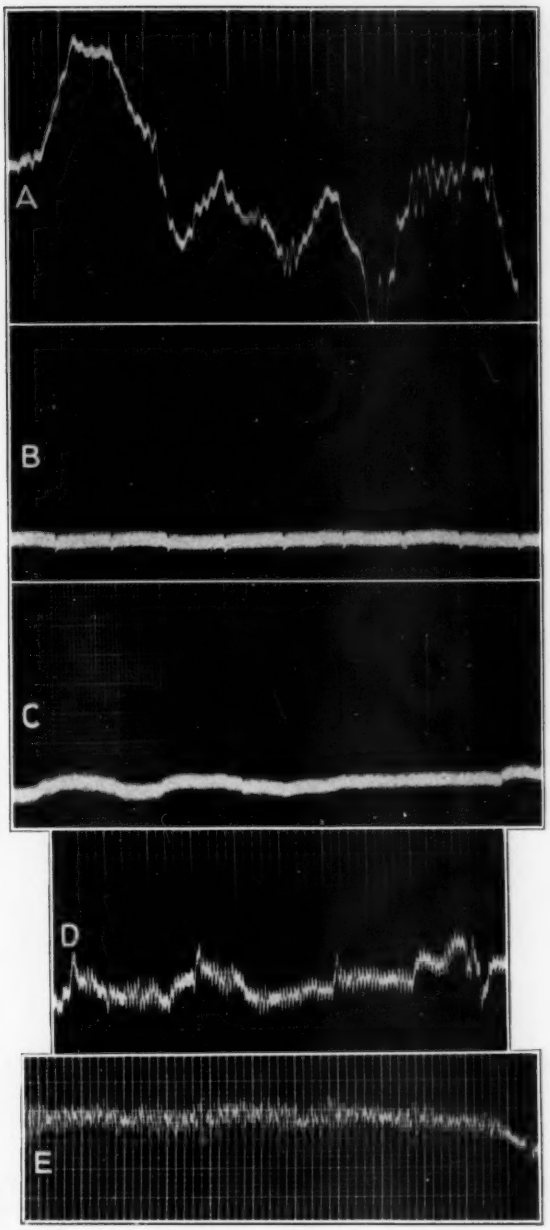

Fig. 4 (case 2).—Electromyographic tracings from the upper portion of the right arm: *A*, on Jan. 28, 1935, before operation; *B*, on February 9, eleven days after operation; *C*, on February 15; *D*, on July 5, and, *E*, on May 4, 1936. In all the tracings the time is indicated in horizontal lines, the smaller intervals representing one twenty fifth and the larger one fifth of a second. In *A* the film moved rapidly, about one-fourth as fast in *B* and *C* and half as fast in *D* and *E*. The sensitivity of the oscillograph was 1 cm. of deflection for each 1.5 millivolts in *A* and 1 cm. of deflection for each 0.3 millivolt in *B* to *E*. In *B* to *D* a 60 cycle fluctuation is seen and in *B* and *D* a slower electrocardiographic fluctuation.

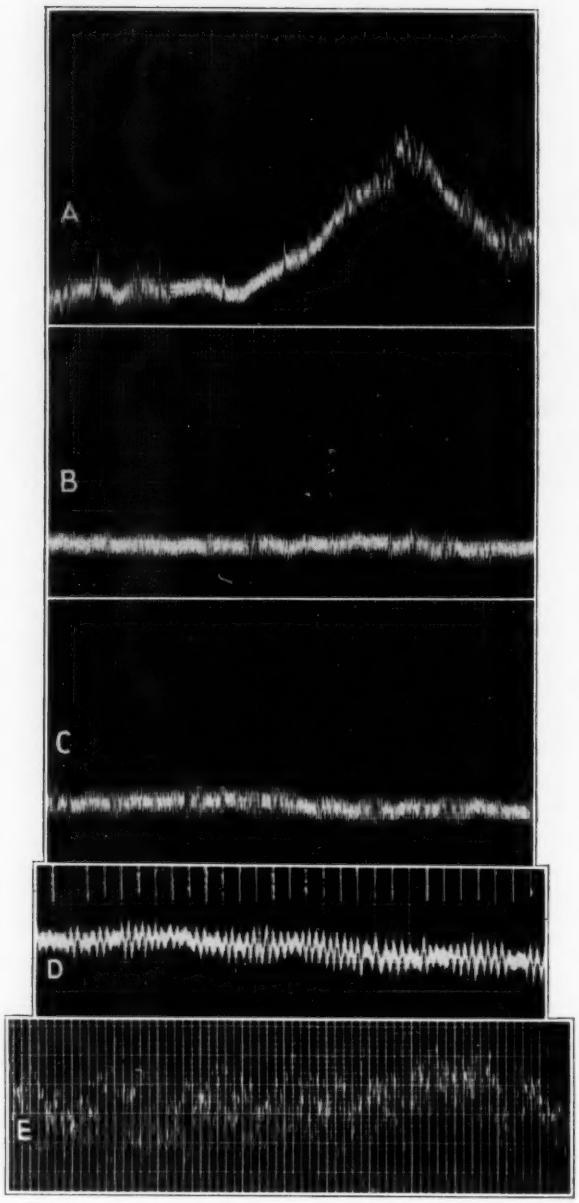

Fig. 5 (case 2).—Electromyographic tracings from the left forearm. The dates on which the tracings *A* to *E* were made were the same as for figures 3 and 4. The time is indicated in the same manner as in the preceding figures. Tracings *A* to *C* were made at the same speed. Tracing *D* was made almost four times as fast; tracing *E* twice as fast. The sensitivity of the oscillograph was 1 cm. of deflection for each 1.5 millivolts in the first four tracings and 1 cm. for each 0.3 millivolt in tracing *E*.

of the left arm, not previously recorded, showed considerable activity with the arm "at rest" (fig. 6*A*), and this was greatly increased with voluntary effort. In the left forearm, although spontaneous activity was somewhat reduced as compared to that recorded preoperatively, it was definitely present (fig. 5*B*).

On the seventeenth postoperative day (February 15) additional electromyographic records were made (figs. 3*C*, 4*C*, 5*C* and 6*B*). There was still practically no evidence of spontaneous activity in the right upper extremity, although considerable electrical activity could be produced by voluntary efforts.

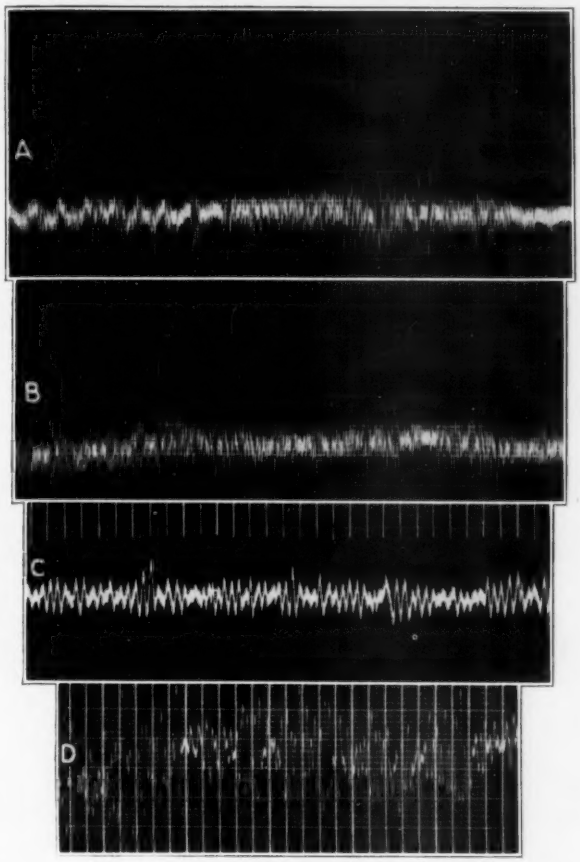

Fig. 6 (case 2).—Electromyographic tracings from the upper portion of the left arm. No tracing was made before operation. Tracing *A* was made on Feb. 9, 1935, eleven days after operation; *B*, on February 15; *C*, on July 5, and *D*, on May 4, 1936. The time is indicated as in the preceding figures. Tracings *C* and *D* were made almost four times as fast as tracings *A* and *B*. The sensitivity of the oscillograph was 1 cm. of deflection for 1.5 millivolts in tracings *A* to *C* and 0.3 millivolt per centimeter in *D*. LLL

In the upper portion of the left arm the spontaneous activity was slightly greater than that recorded on the eleventh postoperative day, and the same was true of the forearm.

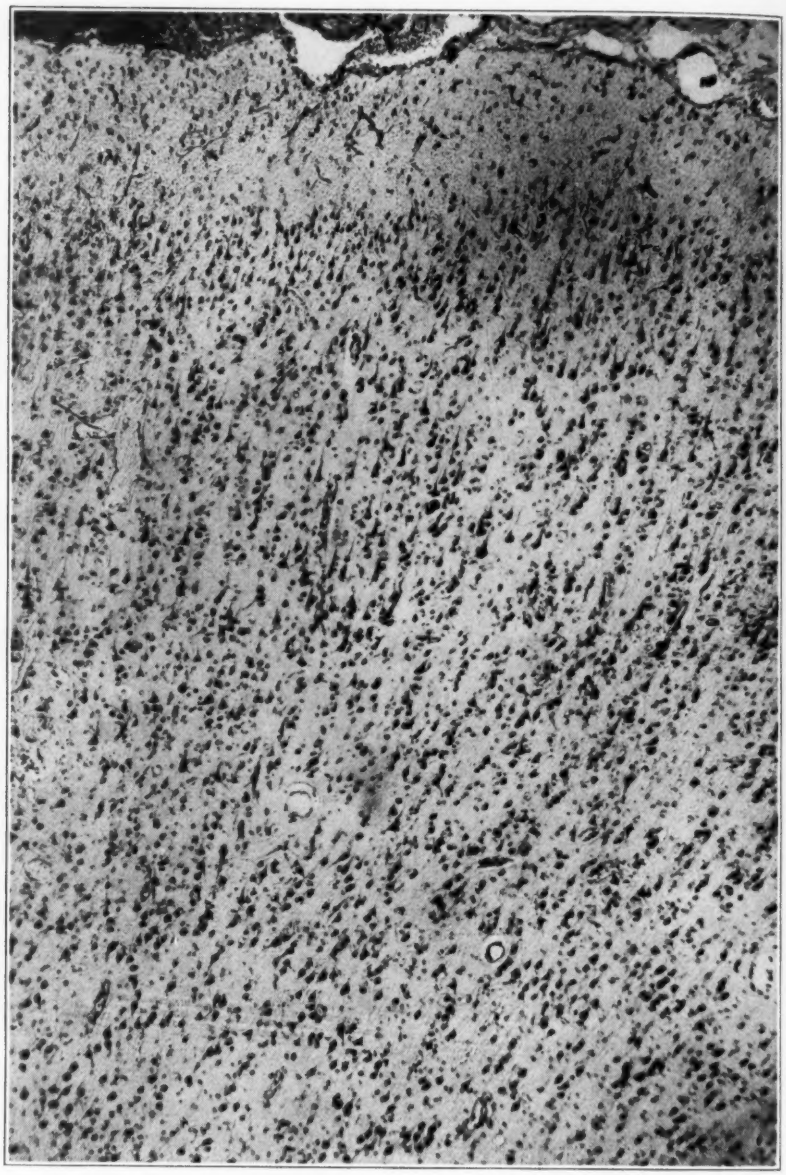

Fig. 7 (case 2).—Photomicrograph of the section of cerebral cortex removed, in an area with some slight pathologic changes. Other areas appeared to be more nearly normal. This is typical cortex of area 6. The reduction in the number of cells in the third layer and the elongated tortuous processes of some of those remaining can be seen. Thionine; × 60.

Tracings made on July 5, about five months after the operation (figs. 3 *D*, 4 *D*, 5 *D* and 6 *C*), revealed slightly more spontaneous activity in the right upper extremity than had been present immediately after operation. The condition in the left upper extremity was relatively unchanged.

Records made on May 4, 1936, fifteen months after the operation (figs. 3 *E*, 4 *E*, 5 *E* and 6 D), revealed considerable involuntary muscular activity in the upper portion of the right arm and in the forearm (figs. 3 *E* and 4 *E*) but much less than was present before operation and also much less than was present in the left upper extremity (figs. 5 *E* and 6 *D*). It will be noted that much more activity was recorded in these last tracings from the left arm (figs. 5 *E* and 6 *D*)

Fig. 8 (case 2).—Photomicrograph as in figure 7, showing more clearly the abnormal ganglion cells. Thionine; × 170.

than was previously seen (figs. 5 *A* to *D* and 6 *A* to *C*), but it will be noted that in making this last tracing the sensitivity of the oscillograph was increased five-fold in order to make the tracing comparable to those taken from the right side.

Microscopic Examination.—Study of the piece of cerebral cortex removed at operation revealed that only in the posterosuperior part did it contain any of area 4 of Brodmann, i. e., the true motor cortex. At this point only, the block included a small portion of the anterior wall of the rolandic fissure. The remainder of the block was composed exclusively of premotor cortex, area 6 of Brodmann (fig. 7). This block of cortex consisted of part of the crest of the precentral gyrus and parts of the posterior portions of the first and second frontal gyri.

In the main the entire piece of extirpated cortex was microscopically normal. There were a few narrow hyperchromatic ganglion cells with long tortuous apical processes (fig. 8) in the third cortical layer of a small area; otherwise no abnormal cells, ganglionic or glial, were seen. The number of cells in layer III in this same abnormal area also seemed to be reduced (fig. 7).

Comment on the Results of Extirpation.—Stimulation of the cortex gave no significant information in this case other than to delimit the area of representation of the right upper extremity and the right side of the face in the precentral gyrus.

The results of the extirpation of the portion of area 6 of Brodmann in which the right upper extremity was represented are instructive. That the piece of tissue removed was almost exclusively from area 6 was clearly shown by the microscopic examination (fig. 7). However, it cannot therefore be concluded that the extirpation left area 4 and its major projection system, the pyramidal tract, essentially in its preoperative state. The trauma which the operation must have caused to such a nearby area and tract undoubtedly resulted in considerable damage. However, that the area was not totally destroyed was evidenced by the amount of voluntary movement which returned after the operation and which was far greater than could be attributed to ipsilateral innervation, as the amount of voluntary movement was much more than occurred in any of the cases of hemidecortication reported in human beings.[10] It appears also that in attempting to spare the "face" area in order to avoid the production of a motor aphasia, part of the "finger" area also was left. This resulted in the early return of some mild involuntary movements to the thumb and forefinger.

The results of the operation may be summarized as follows: (1) motor aphasia, temporary; (2) apraxia of the left hand, temporary; (3) an increase in the right hemiparesis to complete paralysis, largely temporary, and (4) a marked reduction of the involuntary movements in the right upper extremity.

The question of possible reflex grasping, which the patient reported but which we did not observe during his stay in the hospital, and the question of whether spasticity in the right upper extremity was more or less than before operation would best be ignored because of their uncertainty.

It seems that the aphasia and apraxia were the results of trauma to neighboring structures, which probably caused temporary edema.

10. Gardner, W. J.: Removal of the Right Cerebral Hemisphere for Infiltrating Glioma, J. A. M. A. **101**:823-825 (Sept. 9) 1933. Dandy, W. E.: Removal of Right Cerebral Hemisphere for Certain Tumors with Hemiplegia: Preliminary Report, ibid. **90**:823-825 (March 17) 1928; Physiological Studies Following Extirpation of the Right Cerebral Hemisphere in Man, Bull. Johns Hopkins Hosp. **53**:31-51, 1933.

The occurrence of temporary aphasia indicates the persistent dominance of the left hemisphere in regard to speech, even though the patient had been "left handed" from birth. Although the increase in paralysis on the right side largely subsided in a few days, the persistent increased impairment of the leg was probably caused by more severe damage to the pyramidal system than simple edema.

That the disappearance of the involuntary movements was due to the abolition of nervous impulses seems definitely established by this case and is most clearly shown by the electromyograms taken before and after operation. It has occurred to some interested persons that, on purely theoretical grounds, removal of area 6 might reduce or abolish involuntary movements by increasing spasticity in the extremity. That such was not the case here is shown not only by the complete absence of action currents in the involved muscles, as demonstrated in the electromyograms, but even more forcefully by the fact that during the afternoon of the day of operation the right upper extremity was completely flaccid, yet no movements were present in that extremity.

That the abolition of involuntary movements was due to the local removal of the "arm" area of the precentral gyrus and not to the general effects of the operation is clearly established by the fact that involuntary movements were present on the left side almost as soon as the patient recovered from the anesthesia and about the right eye the following morning. This point is also of interest in that it shows clearly that the involuntary movements in the right extremities, at least in this case, arose exclusively in the contralateral cerebral hemisphere. This fact indicates that the ipsilateral innervation from the precentral region, discussed by Fulton and one of us (P. C. B.),[11] does not participate in the production of athetosis.

That the abolition of these movements was due to the extirpation of area 6 rather than area 4, the only two cortical areas which might have been injured, is also indicated for many reasons:

1. Even before operation the patient was suffering from severe paralysis of the right upper extremity which presumably was due largely to a lesion of the pyramidal system, yet severe involuntary movements were present. It is difficult to conceive of the conduction of the impulses required for such movements by a fiber system so seriously damaged. For example, voluntary movements of the fingers were practically impossible, yet the involuntary movements were most violent there.

2. By the use of a large dose of barbiturates the involuntary movements were practically completely abolished, while voluntary movements,

11. Bucy, P. C., and Fulton, J. F.: Ipsilateral Representation in the Motor and Premotor Cortex of Monkeys, Brain **56**:318-342, 1933.

except for finer coordinated movements, remained essentially intact. From this it appears, as previously noted, that area 4 and the pyramidal tract were relatively little affected by the barbiturates. The suppression of the involuntary movements must therefore have been due to the effect of the drug on area 6 and the parapyramidal system.

3. The portion of the cortex removed at operation, removal of which abolished the movements, consisted essentially of area 6, as shown by microscopic examination, although area 4 and the pyramidal tract which arises from it could hardly have been completely spared.

4. After the operation, although the patient recovered volitional movement in the right upper extremity comparable to and even more useful than that present before the operation (this must be interpreted as due to the preservation of the pyramidal system in almost its preoperative state), the involuntary movements returned to only a slight degree and predominantly to the one region, that of the fingers, the representation of which in area 6 was undoubtedly spared in attempting to preserve the "face" area.

It seems, then, that this case further establishes the point made in the study of a previous case, that the involuntary movements of athetosis arise primarily as a result of activity in area 6. Neither this case nor the one previously reported offers any clue as to the nature or location of the pathologic lesion which released area 6 to this pathologic activity.

Recently it has been stated by Walshe [12] that our statement, in regard to case 1 reported with Buchanan,[1] that the "premotor cortex" was removed is incorrect. First, let it be said that the terms "motor cortex" and "premotor cortex" did not appear in that article. Walshe's meaning, therefore, is far from clear. If, however, he used "premotor cortex" as synonymous with area 6, a use to which the term "premotor" has frequently been put, then his statement is obviously incorrect and his criticism unjustified. That the area removed was largely from area 6 is clearly demonstrated and is shown by two facts: First, the area removed was largely from that part of the cerebral cortex which the Vogts [13] have shown to have the cyto-architectonic characteristics of area 6, as described by them and by Brodmann [14] and illustrated by

12. Walshe, F. M. R.: On the "Syndrome of the Premotor Cortex" (Fulton) and the Definition of the Terms "Premotor" and "Motor," with a Consideration of Jackson's Views on the Cortical Representation of Movements, Brain **58**:49-80, 1935.

13. Vogt, O., and Vogt, C.: Allgemeinere Ergebnisse unserer Hirnforschung, J. f. Psychol. u. Neurol. **25**:273-462, 1919.

14. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Principien dargestellt auf Grund des Zellenbaues, Leipzig, J. A. Barth, 1909.

Foerster.[15] This point is clearly shown by a comparison of figures 1 and 3 in the original article.[1] Second, microscopic examination of the tissue removed revealed it to be composed of areas 4 and 6, area 4 occupying a very small posterior part of the piece of cortex removed. This point is clearly illustrated by figures 4 and 5 of the article written with Buchanan.[1]

Walshe stated further that the area removed could not have been the "premotor cortex," as forced grasping did not develop. (The same criticism could probably be applied in the present case.) However, it is to be recalled that no one has shown that destruction of every part of area 6 ("premotor cortex") will result in forced or reflex grasping. In fact, all the evidence presented in cases of human beings, particularly that of Wilson and Walshe [16] and Adie and Critchley,[17] points to the conclusion that the lesion of area 6 must, at least in human beings, be in a specific part of that area, i. e., the posterior portion of the first frontal convolution, a region relatively little injured in our two cases. It is not surprising, therefore, that forced grasping did not develop.

One other point in regard to forced grasping should be made. Forced or reflex grasping is probably the result of the release of some subcortical reflex mechanism from cortical inhibition which all evidence indicates comes from area 6. The presence of forced grasping is therefore dependent on the integrity of this subcortical reflex mechanism which is released by the removal of area 6. The failure of the development of forced grasping after removal of the appropriate portion of area 6 (which was not done nor intended in these cases) may indicate impairment of this subcortical reflex mechanism rather than that destruction of this part of area 6 will not give rise to forced grasping. In healthy experimental animals it may be reasonably supposed that the subcortical reflex mechanism concerned in forced grasping is intact. But in human beings, for whom the nature of the pathologic lesions is undetermined, and practically nothing is known of the anatomic localization of this subcortical mechanism, no such assumption can be made.

REPORT OF A THIRD CASE

The following case serves in the main to confirm the detailed observations recorded in the preceding case. However, this case brings out one point not previously illustrated, the possibility that the involuntary

15. Foerster, O.: Ueber die Bedeutung und Reichweite des Lokalizationsprinzips in Nervensystem, Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 46, 1934, pp. 117-211.

16. Wilson, S. A. K., and Walshe, F. M. R.: The Phenomenon of "Tonic Innervation" and Its Relation to Motor Apraxia, Brain **37**:199-246, 1914.

17. Adie, W. J., and Critchley, M.: Forced Grasping and Groping, Brain **50**:142-170, 1927.

movements of athetosis originate from area 4 (not the Betz cells or pyramidal tract) as well as from area 6. Recently, Levin [6] has demonstrated that, exclusive of the pyramidal tract which arises from the Betz cells of area 4, the efferent projection systems of areas 4 and 6 are similar in course and termination. For these nonpyramidal projection fibers the term parapyramidal has been suggested.[18] Anatomically, there is no known difference between the parapyramidal fibers which arise from area 4 and those from area 6. Detailed information concerning their functional differences and similarities is not available. A priori, however, it appears reasonable that if the involuntary movements of athetosis are produced by impulses passing over the parapyramidal system from area 6, the same movements could be evoked over the parapyramidal fibers from area 4. Both case 1 and case 2, with the severe hemiparesis and with the deep extirpations which were made, are poorly designed to test that possibility. In the following case the extirpation was much more superficial, and a definite effort was made to preserve area 4 and its projection systems.

It is timely to point out here that, whereas area 4 is relatively large as compared with area 6 in the monkey (Macaca mulatta, the species studied by Levin [6]) and therefore contributes heavily to the parapyramidal system, in man area 4 is relatively much smaller than area 6,[19] and its contribution to the parapyramidal system would therefore be expected to be much less than that from area 6. It is thus to be expected that the parapyramidal system arising from area 4 in man plays a lesser rôle than do comparable fibers in the monkey and, furthermore, than do the more abundant parapyramidal fibers from area 6 in man. It would be expected that leaving area 4 relatively intact in a case of athetosis, while removing area 6, would result in greatly reducing the intensity of the athetoid movements without completely abolishing them. That is what occurred in case 3.

This observation has led to the conclusion that area 4 as well as area 6 should be extirpated unless there is some contraindication. When there is reason to believe that some useful function of the affected member may be preserved, it will probably be best to leave area 4 intact, as the surviving involuntary movements are slight.

CASE 3.—*Left hemiparesis and hemiathetosis developed at 9 months; examination revealed mental retardation, dysarthria, left spastic hemiparesis, involuntary*

18. Bucy, P. C.: Areas 4 and 6 of the Cerebral Cortex and Their Projection Systems, Arch. Neurol. & Psychiat. **35**:1396-1400 (June) 1936.

19. Bucy, P. C.: Frontal Lobe of Primates: Relation of Cyto-Architecture to Functional Activity, Arch. Neurol. & Psychiat. **33**:546-557 (March) 1935; A Comparative Cyto-Architectonic Study of the Motor and Premotor Areas in the Primate Cortex, J. Comp. Neurol. **62**:293-331, 1935.

movements of left side of face and left arm and recurrent dislocation of left shoulder. A large dose of barbiturates abolished involuntary movements, leaving voluntary movements intact. Practically normal encephalogram. Operation: Stimulation of "arm" and "face" areas; abolition of respiratory movements; marked thickening of pia-arachnoid; extirpation of "arm" and "face" areas of area 6. Involuntary movements were abolished at first but returned to a slight degree later.

P. V., who was born on Jan. 24, 1909, was first admitted to the University of Chicago Clinics on March 8, 1935, at the age of 26. He was definitely retarded mentally, and few of the details of his illness could be obtained from the family; hence the following history is brief and probably incomplete.

Birth is said to have been normal, and the child was regarded as a normal infant until a "cold" developed when he was 9 months of age. After that the left side of the face, the left arm and the left leg became paralyzed, and involuntary movements appeared in the involved members. The patient stated that his condition remained unchanged up to the time of his admission to the hospital. Because of marked inversion of the left foot the patient had great difficulty in walking until this deformity was corrected by an orthopedic operation at another hospital in 1931.

The patient had measles and chickenpox during childhood. Tonsillectomy was performed when he was 16.

The patient stated that his brother, aged 36, had had difficulty in walking since birth, owing to a disability of the left lower extremity. He was said to show involuntary movements, not as severe as those of the patient, of the left side of the body. This brother's daughter, aged 6 years, also had a disability of the left lower extremity of recent origin, which had been attributed to anterior poliomyelitis.

Examination.—The patient was a well developed and well nourished Slav. He was definitely retarded mentally. There were evident dysarthria and irregularity of speech. There was definite paresis of the left lower portion of the face, but it was impossible to judge how complete the deficit of voluntary movement was because of the constant involuntary movements of the face, which were most severe about the mouth. Voluntary movement of the forehead and eyelids was practically normal. No motor deficit or involuntary movement was detected on the right side.

Examination of the other cranial nerves revealed that the visual acuity and visual fields were normal. There was some increase in glial tissue along the vessels, but the fundi showed no other changes. The pupils were normal. Ocular movements were full and normal. Sensation over the face was intact. There was no impairment of hearing. Little movement of the soft palate or pharynx was seen on phonation. The tongue was protruded in the midline, but its voluntary control was defective. The patient most commonly sat with his left hand behind his head. In this position the left shoulder was considerably elevated, and the head was turned slightly to the right. He was able to move the left shoulder and elbow voluntarily but with difficulty, and the movements were coarse and ataxic. Voluntary movement of the fingers and wrist was almost absent. The fingers were usually strongly flexed into the palm and could be extended by the patient with his right hand or by the examiner with considerable difficulty. Once extended, the fingers remained in that position only for a short time. If while the fingers were extended an object was placed in the hand, the fingers would close on it quickly and forcibly, and the patient would be unable to relax the grasp. There was a marked increase in resistance to passive movement, greater in the flexors in the left upper extremity.

There were constant, slow, purposeless involuntary movements of the left upper extremity. The hand was often thrown into a characteristic position by the involuntary movements, the wrist being slightly flexed and the fingers hyperextended at the metacarpophalangeal joints and flexed at the terminal phalanges. The left shoulder was frequently dislocated by the involuntary movements; it could be dislocated at will, and the dislocation was then reduced voluntarily. These manipulations of the shoulder joint were not associated with any discomfort.

The left upper and lower extremities were definitely smaller than the right.

There was considerable inversion of the left foot, but this had been corrected sufficiently to permit the patient to walk on the ball of the foot in a pes equinus position. In walking the patient demonstrated a more or less typical spastic hemiplegic limp. There was a definite increase in resistance to passive manipulation of the left leg, especially in the extensor muscles.

Involuntary movements were much less severe and extensive in the left lower extremity than in the left upper extremity. They consisted of slow, purposeless, bizarre involuntary movements of the foot and toes, especially the great toe. There were no involuntary movements in the right extremities.

All tendon reflexes were hyperactive on the left side, especially in the lower extremity. Because of the involuntary movements of the great toe, the response to plantar stimulation was not positively determined on the left, though there was a powerful defense (flexor) reflex. The response was normal (plantar flexion) on the right. The tendon reflexes on the right were normal.

Sensation of all modalities was everywhere intact.

Diagnosis.—The diagnosis was left hemiathetosis and left spastic hemiparesis of unknown etiology.

Effect of Barbiturates.—On March 12, at 11:45 a. m., the patient was given 7½ grains (0.45 Gm.) of pentobarbital sodium. This made the patient somewhat drowsy, but he was still awake. Voluntary movements were still present, *but all involuntary movements were abolished.* No examination of fine coordinated movements was made. At 12:20 p. m. 4 grains (0.24 Gm.) of soluble phenobarbital U. S. P. (sodium phenobarbital) was given subcutaneously. The patient soon lost consciousness, and an encephalogram was made.

At 4:30 p. m. the patient was again examined. He was soundly asleep, and the examination did not awaken him. There were no involuntary movements. There was definite "springlike" resistance to passive extension of the left elbow, wrist and fingers, probably due to contracture of the muscles and fibrous changes about the joints.

At 11 a. m. the following day, almost twenty-four hours after the administration of pentobarbital sodium, the patient was awake and alert. All voluntary movements previously present were possible; no note as to fine coordinated movements was made, but there were practically no involuntary movements.

Encephalogram.—An encephalogram was made after the removal of 150 cc. of cerebrospinal fluid and the injection of air. The roentgenograms revealed only a mild increase in the amount of air in the subarachnoid spaces over the cerebral hemispheres. The ventricular system appeared normal.

Operation.—The patient was operated on on March 14 under light ether anesthesia. The usual osteoplastic flap was reflected, exposing the posterior portion of the right frontal lobe except the most superior part. The pia-arachnoid membrane was grossly abnormal, especially over the exposed portions of the second and third frontal convolutions, and much less abnormal over the precentral gyrus. Over the parietal lobe it seemed normal. The membrane was thick and

milky, and over the second and third frontal gyri it was entirely opaque. The amount of fluid in the subarachnoid space anterior to the precentral gyrus was greatly increased over normal. The entrapped fluid was released, and a map of the exposed cortex was drawn by Dr. Douglas N. Buchanan. The cortex was then stimulated with a weak faradic current, a monopolar electrode being used, and the results were recorded on the map. Stimulation of the precentral gyrus only gave response. The "leg" area had not been exposed. Discrete movements were elicited in the shoulder, pectoral muscles, elbow, hand and face, as indicated in figure 9. In the ventral portion of the precentral gyrus, just a few millimeters anterior to the rolandic fissure and in the lower part of the "face" area, was a small, sharply localized area stimulation of which caused cessation of the respiratory movements. The first stimulus was slightly above the threshold for movements in the extremities and face but not of greater intensity than had been used in other parts of the brain without effect on the respiration. This stimulus

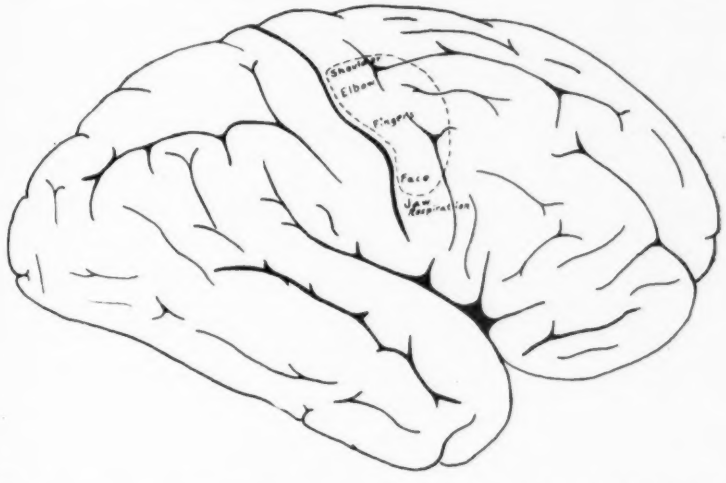

Fig. 9 (case 3).—Diagrammatic summary of the results of electrical stimulation of the cerebral cortex. The point marked respiration is the area from which cessation of respiratory movements was evoked. The broken line encloses the area extirpated.

lasted for about five seconds. Respiratory movements ceased immediately at the onset of stimulation, and the cessation persisted for about fifteen seconds after the termination of the stimulus. The intensity of the stimulus was then reduced, and cessation of the respiratory movements was produced which did not outlast the stimulus.[20]

The cortex of that portion of the precentral gyrus containing the representation of the face and upper extremity (except the anterior wall and lip of the rolandic fissure and the "respiratory" area) and the neighboring parts of the second and third frontal convolutions were removed for a depth of 5 or 6 mm. Where the cortex dipped in deeper along sulci, it was removed with a suction

20. This experiment has been briefly recorded by P. C. Bucy and T. J. Case (Cortical Innervation of Respiratory Movements, J. Nerv. & Ment. Dis. **84**:156-168, 1936).

apparatus. The posterior margin of the block was sloped anteriorly in order to preserve area 4 intact if possible. The area of extirpation measured 4 by 2.25 cm. on the surface (fig. 9).

Postoperative Course.—At 4 p. m. on the day of operation the patient was awake and alert. Speech was unchanged. There was definite weakness of the left lower portion of the face. The patient was able to move the left arm forcefully at the shoulder and to extend the elbow. He was unable to flex the elbow or to move the wrist or fingers. There were no involuntary movements of any kind. At 6:30 p. m. he was able to flex the elbow moderately well. He could flex the wrist slightly, but extension was not possible. He could also flex the fingers slightly but not extend them. No involuntary movements were present.

First Postoperative Day (March 15): There were no involuntary movements. Free and extensive movement of the left shoulder, fair flexion and extension of the elbow and weak flexion and very weak extension of the fingers were noted. The resistance to passive movement was definitely greater than normal but much less than before operation. Resistance was most marked in the flexors, and the posture was flexor. Forced grasping could not be elicited.

Fourth Postoperative Day (March 18): No involuntary movements were present. The status of the left upper extremity was practically unchanged.

Fifth Postoperative Day (March 19): The patient was up in a wheel-chair.

Seventh Postoperative Day (March 21): Slight involuntary movements of the left fingers appeared.

Eleventh Postoperative Day (March 25): The patient was walking about. There were no involuntary movements with the arm at rest, but voluntary movements were awkward and crude.

Thirteenth Postoperative Day (March 27): The patient was discharged from the hospital.

Twenty-Fourth Postoperative Day (April 7): The patient was readmitted to the service of Dr. D. B. Phemister for operation to prevent dislocation of the shoulder. Examination revealed occasional slight twitching of the left corner of the mouth and at times some mild involuntary movements of the left hand and fingers.

Twenty-Sixth Postoperative Day (April 9): A Nicola operation to prevent dislocation of the left shoulder was performed by Dr. Phemister, and a cast was applied to the entire left upper extremities, only the fingers being left exposed.

Thirty-Fifth Postoperative Day (April 18): Slight involuntary movements in the fingers continued. The patient was discharged from the hospital with the cast in place.

Subsequent Course.—On September 18, six months after the operation on the brain, the left upper extremity was at times practically free from involuntary movements. Usually, however, some slow, sinuous movements were present in the wrist and fingers. There was practically no involuntary movement in the face, only slight and occasional movement at the shoulder and none at the elbow. Voluntary movements were free and extensive at the left shoulder and elbow but present to only a limited degree at the left wrist and in the fingers. No useful movement of the left hand was present. There was no spasticity at the elbow or shoulder, but spasticity of the flexors of the wrist and fingers was marked. The tendon reflexes were all increased on the left side. Any object placed in the left hand was forcefully grasped, and the patient was unable to release that grasp. This condition was the same as before the operation.

One month later, on October 16, practically no involuntary movement was present.

On Feb. 19, 1936, the patient was again seen. While he was sitting quietly or walking, no involuntary movements were observed except occasional slight twitching of the left angle of the mouth. Twitchings about the eye were not seen. Whenever he attempted to move the left forearm voluntarily (such movements were crude and awkward), moderate spontaneous involuntary movements of the entire left upper extremity appeared. Compared with the preoperative state, his condition was much improved.

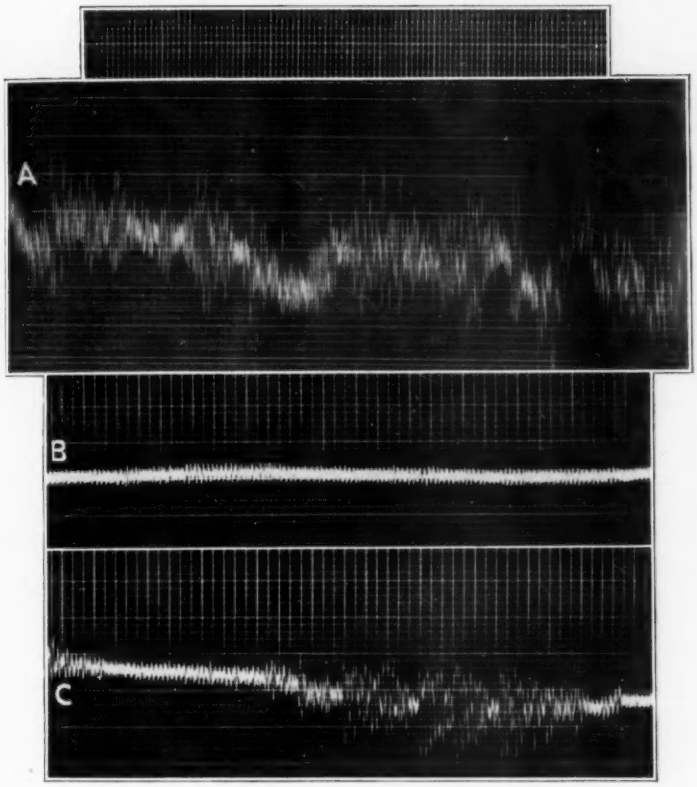

Fig. 10 (case 3).—Electromyographic tracings from the upper portion of the left arm: *A*, March 11, 1935, before operation, and *B* and *C*, on May 19, 1936, fourteen months after operation. The timing is indicated by vertical lines. The smaller intervals represent one twenty fifth of a second. In *A* a strip from another record at the same speed has been shown for reference, as the time marker was inadvertently left off this record. The film was moving twice as fast in *B* and *C* as in *A*. The sensitivity in all instances was 1 cm. of deflection for 1.5 millivolts.

When he was last seen, on May 19, 1936, fourteen months after the operation, his condition was much the same as already noted. When he was sitting at rest there were practically no involuntary movements. Any excitement or volun-

tary effort resulted in the appearance of some movements in the left side of the face and left arm, though they were by no means as severe as before operation. However, in view of the fact that this patient's involuntary movements prior to operation were much less severe than those in case 2, it seems that the degree of improvement in this instance was definitely less.

Electromyograms.—As in case 2, electromyographic tracings were made from the involved extremity. Those made on March 11, 1935, prior to operation, revealed definite evidence of severe spontaneous involuntary muscular activity (figs. 10 *A* and 11 *A*). Unfortunately no tracings were made for some time after operation. Tracings made on May 19, 1936, a little over fourteen months after the operation (figs. 10 *B* and *C* and 11 *B*), revealed definite evidence of

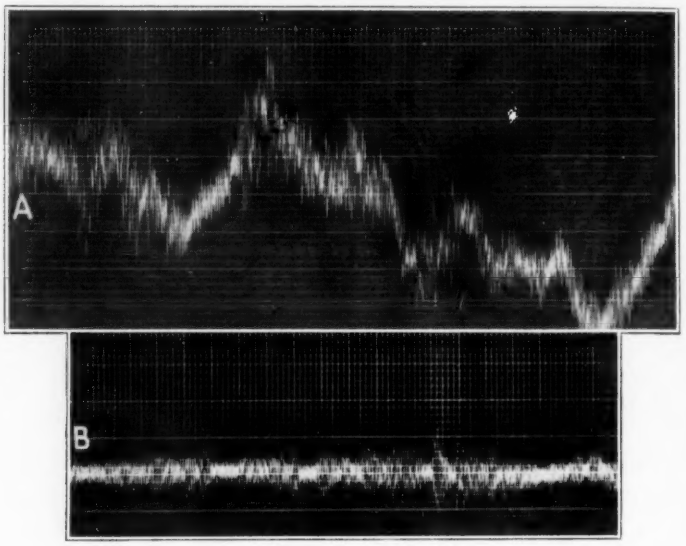

Fig. 11 (case 3).—Electromyographic tracings from the left forearm: *A*, on March 11, 1935, before operation, and, *B*, on May 19, 1936, fourteen months after operation. The timing was the same in the two records. The smaller intervals represent one twenty fifth of a second and the larger ones one fifth of a second. The sensitivity was 1 cm. of deflection for 1.5 millivolts in both tracings.

spontaneous muscular activity, though of less severity than before operation. As is clearly shown in figure 10 *B* and *C*, there were periods when no involuntary muscular activity was present, but these were not infrequently interrupted by sudden bursts of activity.

Microscopic Examination.—The piece of cerebral cortex removed revealed what appeared to be area 6. No Betz cells were present. The extirpated cortex was far from normal. It was much less cellular than normal cortex, apparently owing to the death of many of the ganglion cells (fig. 12). Many of the cells which remained were swollen and rounded and had pale granular cytoplasm (fig. 13). Still other cells were elongated and slender, with dark hyperchromatic cytoplasm.

The pia-arachnoid membrane was much thickened and contained numerous blood vessels with thickened walls but a normal endothelial lining. The subarachnoid space was largely obliterated. In some places the meninges were infiltrated with lymphocytes, polymorphonuclear leukocytes and macrophages. There was no perivascular cellular infiltration.

Comment.—The abolition of the involuntary movements both by the barbiturates and by the extirpation of area 6 has been fully discussed in connection with case 2. The same points apply in the present instance, and only one point is of concern here. No effort was made in this

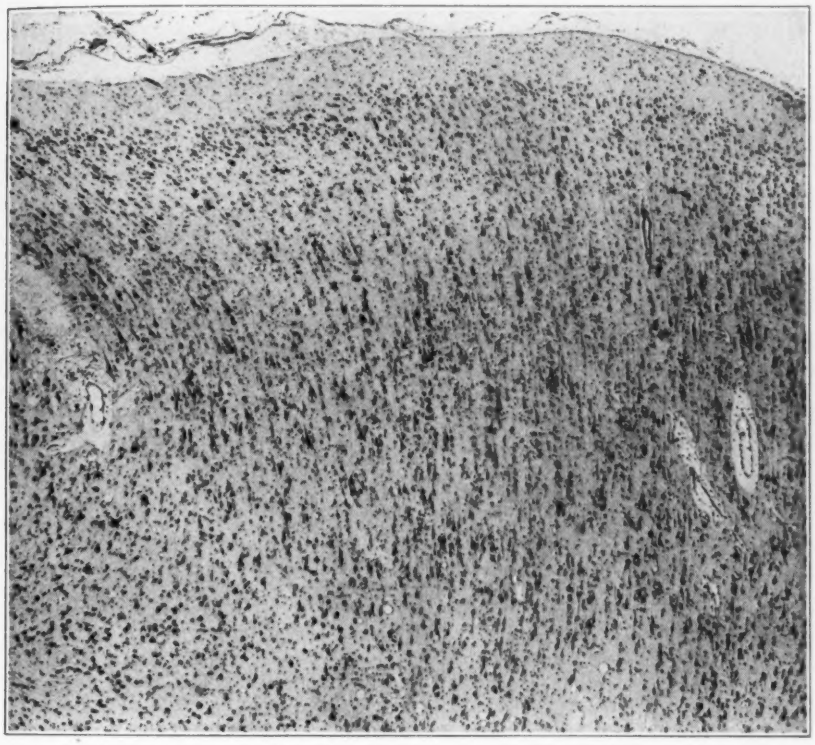

Fig. 12 (case 3).—Photomicrograph of an area in the extirpated piece of cerebral cortex, apparently from area 6. Many ganglion cells have fallen out. Thionine; × 35.

instance to preserve the representation of the face; in fact, it was deliberately extirpated. Thus, it is impossible that the representation of the fingers was preserved in area 6, as we believe probably occurred in part in case 2. On the other hand, area 4 for both "arm" and "face" was carefully preserved. Although immediately after the operation no involuntary movements were present, they were subsequently observed to occur occasionally and in a mild form. As it has been shown that in case 2 the involuntary movements arose exclusively from the contra-

lateral cerebral cortex and as area 6 had been extirpated from the hemisphere opposite to the hemiathetosis, it appears that the cortex left behind along the anterior lip of the rolandic fissure, i. e., area 4, must have been responsible for the slight involuntary movements seen after the operation. It is therefore concluded that the involuntary movements of athetosis which arise largely from area 6 may in a small measure arise from that portion of the parapyramidal system which finds its origin in area 4.

SUMMARY AND CONCLUSIONS

Two cases of athetosis are presented: one of much more severe athetosis on one side, the other of strict hemiathetosis. In both instances

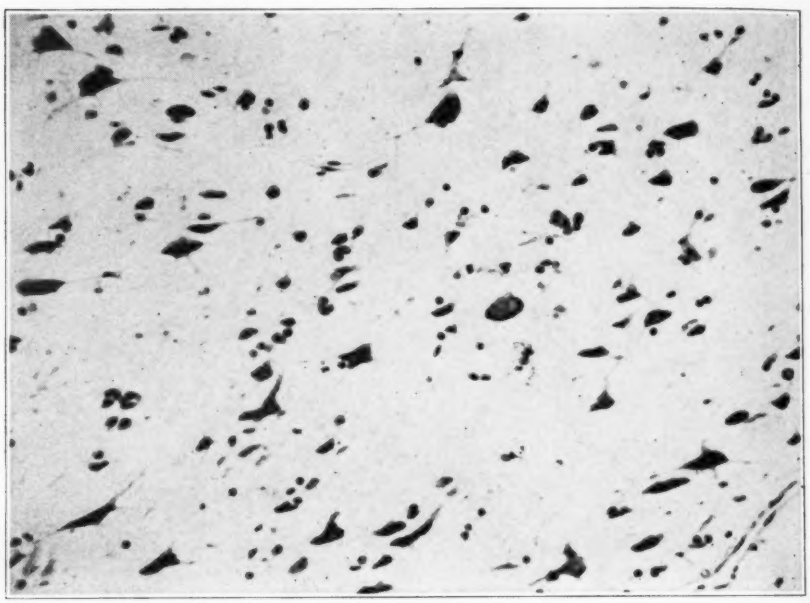

Fig. 13 (case 3).—Photomicrograph from the same region as shown in figure 11. The reduction in the number of ganglion cells and the abnormality of some which remain is seen. Thionine; × 235.

a large dose of barbiturates temporarily abolished the involuntary movements, leaving the voluntary movements more or less intact. In both instances extirpation of the "arm region of area 6" resulted at first in complete abolition of the involuntary movements, which later returned to a mild degree. In case 2 this was attributed to the sparing of part of the representation of the fingers in area 6; in case 3, to the careful sparing of all of area 4. From these observations it is concluded that (1) the involuntary movements of athetosis are projected largely from area 6; (2) the parapyramidal fibers from area 4 may participate to

some slight extent in the production of these movements, and (3) in suitable cases of hemiathetosis, or of athetosis predominating on one side of the body, extirpation of the contralateral area 6 or areas 4 and 6 is an appropriate therapeutic procedure which gives gratifying results.[21]

No conclusions are drawn as to the relationship between the abnormalities observed in the cerebral cortex in these cases and the development of athetosis. Nor has any conclusion been drawn as to the nature or location of the lesions responsible for the appearance of the abnormal activity of the parapyramidal system of areas 4 and 6 which gives rise to the involuntary movements of athetosis.

NOTE.—The following discussion applies only to the case of R. E. W. (case 2 of this paper), which was presented with the aid of motion pictures before the American Neurological Association.

DISCUSSION

DR. ERNEST SACHS, St. Louis: I am much impressed in the first place with the result of the administration of pentobarbital sodium, and I hope that Dr. Bucy will state how long the effect lasted after each administration. One technical point which I think is extremely interesting and important involves the limits of area 6. There is some difference of opinion between Foerster, Hines and Fulton as to the limits of area 6 in the human brain. The operation I have performed, as originally suggested by Horsley, consists in removing one entire precentral convolution and carrying the incision down to the bottom of the sulcus in front and behind it. I thus remove a less extensive area than Dr. Bucy does, and though I undoubtedly remove some of area 6, especially that portion which affects the shoulder and the arm, I do not remove all of it. This may well explain the difference in the results that I have obtained in instances of athetosis and focal convulsion, for in my cases I believe that the voluntary return of function has been more nearly complete.

Dr. J. F. FULTON, New Haven, Conn.: Do you carry the incision down to the bottom of the central sulcus?

DR. E. SACHS, St. Louis: Yes.

DR. J. F. FULTON, New Haven, Conn.: You attempted, did you not, to remove all of the area gigantopyramidalis and not to encroach too far cephalad on the premotor area?

DR. ERNEST SACHS, St. Louis: As I showed in the diagram, I go right to the bottom of the sulcus. I have tried in the past to avoid the caudal part of the convolution in front.

DR. S. COBB, Boston: I am interested in Dr. Bucy's remarkable result. I should like to comment, however, that the patient was not suffering from

21. Since the report of case 1 by Bucy and Buchanan[1] in 1932, Dr. Ernest Sachs has recorded three additional cases of unilateral athetosis in which extirpation of the appropriate portion of the contralateral precentral gyrus resulted in cessation of the involuntary movements (The Subpial Resection of the Cortex in the Treatment of Jacksonian Epilepsy [Horsley Operation] with Observations on Areas Four and Six, Brain **58**:492-503, 1935).

athetosis. The moving picture shows that he had a rapid rhythmic movement. Athetosis is a slow squirming movement.

DR. J. M. NIELSEN, Los Angeles: Dr. Bucy pointed out that the patient had apraxia of the left hand for several days. I should like to call attention to the fact that the condition in this case was a beautiful example of Liepmann's conception of apraxia. There was kinetic apraxia, according to Liepmann's classification, in the right hand and sympathetic apraxia in the left hand from a very small lesion, which fits in perfectly with the old conception of apraxia.

DR. T. J. PUTNAM, Boston: Dr. Bucy is to be complimented on this excellent surgical result and particularly on the thoroughness with which the case has been reported. It seems to me that the physiology of the involuntary movement in general is difficult to understand and that physicians badly need careful studies, especially of cases in which there has been surgical intervention.

I was impressed, as was Dr. Cobb, with the fact that the condition in this case differs from that in some instances of athetosis. This implicates classification and nomenclature, and I have an idea that the present methods of classification are inadequate and that the matter should be left open. An interesting fact is that this is a type of abnormal movement associated with hemiplegia which was relieved by ablation of the cortex.

It is difficult for me to understand what the relationship is between the result obtained by ablation of the cortex and that obtained by section of the extrapyramidal tracts in the cord, which produces much the same sort of change in that the extremity is often paralyzed for days after the section of the tracts and that there is usually a greater degree of relief at first than there is later. Does this mean that the two are identical, that neurosurgeons are interfering with nerve cells in the cortex, the axons of which might be cut in the cervical portion of the cord, or is there some sorting out farther down the cord?

Dr. Bucy's diagram leads me to believe that some of the cells which were interfered with also send their axons down the pyramidal tracts as well as down the extrapyramidal system. I should like to ask if that is his impression.

In the series of twelve or thirteen cases in which I have sectioned the ventral portion of the spinal cord, I have been searching for a case in which I should feel justified or impelled to do the Horsley operation in place of chordotomy. For one reason or another I have not felt justified in doing this, either because the involvement was unilateral or because there was some use of the affected hand. I have made encephalograms in practically all these cases in an attempt to find some evidence of disease of the precentral region corresponding to the member or members involved. In only one case did there seem to be definite evidence in the encephalogram of local cortical atrophy, and in that instance it was present on both sides of the central sulcus. I should particularly like to ask Dr. Bucy in the second place whether it is his experience that in these cases the cortex is abnormal and whether any abnormality can be demonstrated in the encephalogram. It seems to me that if one could find a typical encephalographic picture it might be a step forward in a practical classification of these diseases.

My own results with encephalography have not been encouraging in this direction. In general, they show merely a lowering of the floor of the lateral ventricle on the affected side, and, as I say, it is usually impossible to tell where in the basal nuclei the lesion lies. In most instances I have not observed any atrophy of the cortex.

I should like to comment also on the fact that the barbiturates stop the involuntary movements and permit voluntary ones to continue. In my experience this is unusual. I think perhaps all those present have observed patients with paralysis agitans who believed they were much better and who seemed to be

demonstrably much quieter after a few drinks of alcoholic liquor. Sometimes the ordinary sedatives seem to work well in certain instances of paralysis agitans. I have not seen any such striking results in athetosis. Indeed, I have been rather struck by the fact that when the subject is under the influence of an anesthetic (usually tribromethanol in amylene hydrate), for example, in encephalography, the involuntary movements persist long after the voluntary ones are abolished. Indeed, this is one of the torments of performing laminectomy in these cases. One does not dare to have deep anesthesia, and light anesthesia may allow the involuntary movements to persist.

Is it conceivable that this may be a practical differential point in forming a workable therapeutic classification of these diseases? I am thinking, of course, that this is possibly related to the fact that the movements in this instance were more rapid and were more nearly of an alternating type than those in the classic type of athetosis.

Dr. W. F. Schaller, San Francisco: I was much interested in the motion pictures from the diagnostic standpoint. As I was sitting in the dark, I translated myself back into the motor menagerie of the Salpêtrière and Pitres when I was a student. I think that the condition in this case presents evidence of athetosis; the vermicular movements of extension and flexion are rather characteristic. I do not think it is an instance of pure athetosis. It might be classed as choreo-athetosis, with predominance on one side.

I do not know how to interpret the rapid rhythmic movements stressed by Dr. Cobb. The action of the right upper extremity suggests hemiballismus. I am sure that the condition presents evidence of a complicated motor lesion. I remember a patient in the clinic of the Stanford University Hospital who demanded amputation of an extremity because it was wholly outside her control; her arm flew around in an embarrassing manner. She anchored it behind her back in order to get it out of her way. We amputated the arm finally. That was before surgical intervention in the central nervous system had been suggested for the alleviation of these abnormal movements of complicated pattern.

Dr. Roland P. Mackay, Chicago: I should like to ask Dr. Bucy one or two questions. In the first place, what was the state of the tendon reflexes in the affected limb prior to operation, and what was the effect of the operation on these reflexes? In the second place, what was the state of tone in the affected limb prior to operation, and what was the effect, if any, of the operation on that state of tone? I should like particularly to ask regarding the presence of a so-called cog-wheel phenomenon in the limb and whether or not that phenomenon, if it was present, was altered in any way by the operation.

I noticed in the motion pictures that subsequent to the operation there appeared to be some atrophy in the hand. I should like to ask whether the atrophy, if it was indeed atrophy, was present prior to the operation and whether or not the operation produced any change in that regard.

Finally, may I ask whether the return of voluntary power following the post-operative paralysis was commensurate with the return of the tremor or was greater than the return of the tremor noted subsequent to the operation?

Dr. W. Penfield, Montreal, Canada: No mention has been made in the discussion of the improvement of the condition of the ipsilateral limb. Perhaps Dr. Bucy will comment on that and state whether he considers that area 6 (if that is the area he removed) has a bilateral influence.

Dr. H. C. Naffziger, San Francisco: Knowing of Horsley's work, I operated about twelve years ago on four patients and injected ethyl alcohol into the precentral cortex. The condition of the first patient was almost identical in type

with that of the patient Dr. Bucy has shown, except that, in addition, he had marked bilateral involvement of the muscles of the shoulder girdle. Both arms waved about, so that he was unable to travel on a street car. He had never been able to perform a useful act with his upper extremities, but he could walk about with the same difficulty as Dr. Bucy's patient did. At the time of operation, I did not resect the cortex but after stimulation injected ethyl alcohol to a depth of about 1.5 or 2 cm., paying particular attention to the area controlling the shoulder but also injecting alcohol into the areas controlling the arm and face. The paralysis of these parts was complete for several days, and then voluntary movements gradually returned. At the time of leaving the hospital (in about two and one-half weeks) the patient was able to put his shoes on and tie them, and he had no return of the irregular movements. At the end of another week, when he came back to see me, he was having a little involuntary movement of his hand. Two weeks later the movements were more marked, and at the end of six weeks they were still more so. The irregular movements of the muscles of his shoulder had not returned. His mother was much pleased because he could help himself in eating and could dress himself. Because of the return of involuntary movements of the hand I exposed the cortex again and found its appearance to resemble that of Swiss cheese. After stimulation I injected alcohol into a still wider area. This time the paralysis lasted longer, but voluntary power returned ultimately to the same degree as after the first operation. In spite of the extensive alcoholization of the cortex, some involuntary movement returned in the hand, wrist and forearm. Notwithstanding this, the patient has at the time of this report earned his living as a newsboy for more than eleven years and is able to dress himself and to travel about alone.

I was much encouraged by this result and operated on three other patients with conditions of a similar type. I injected alcohol into large areas, as I had in the two operations on the first patient. The state of those patients three or four months after operation indicated insufficient improvement to make me feel that continuance of the procedure was worth while. In other words, in only one of the four instances did the result seem good enough to warrant the procedure.

DR. J. F. FULTON, New Haven, Conn.: Dr. Sachs has raised the question of whether it would be preferable to remove area 4, that is, the area gigantopyramidalis or area 6, the premotor region, in such cases. According to Kinnier Wilson, tremor and involuntary movements result from cortical motor innervation in the absence of an adequate subcortical system, cerebellar or striatal. In the case of cerebellar tremor, destruction of the pyramidal innervation at the cortical level, that is, removal of area 4, causes immediate and enduring diminution of cerebellar tremor. Integrations from the cortical level after removal of area 4 are carried out with much less marked tremor than is present when area 4 is intact. On the other hand, when area 6 is removed after the occurrence of a cerebellar lesion, cerebellar symptoms, in animals at least, are increased.

If this same reasoning should apply to the striatal lesions producing choreiform and involuntary movements, it would follow, I think, that removal of area 4, such as Dr. Sachs has described with destruction of pyramidal innervation, should be expected to give a more enduring effect on these involuntary movements than removal of area 6. We have not been able to produce in animals these involuntary movements through lesions of subcortical systems, and it is impossible as yet to offer experimental evidence on the subject. I think that adequate experimental evidence must come from the neurosurgeon. It would be interesting to compare a group of cases in which isolated destruction of area 4 had been carried out

with a group of cases, such as that which Dr. Bucy has described, in which the predominant lesion has been in area 6. In Dr. Bucy's case it was a mixed lesion, the cephalic part of area 4 probably being involved, as well as the caudal part of area 6.

DR. P. C. BUCY, Chicago: I shall do my best to reply to this extensive and gratifying discussion. I do not know how well I shall succeed.

The question of what to call the disorder which I have demonstrated has been of no little concern to me. I agree with Dr. Cobb that the condition is not identical with classic athetosis. Yet that designation seems the most appropriate. To refer to these movements simply as being involuntary or hyperkinetic could lead only to greater confusion. The terms choreo-athetosis and hemibalismus are not more accurately descriptive. Certainly the condition has much in common with other forms of athetosis. It is associated with severe hemiparesis. The movements are involuntary, and although many of them are rapid and more or less rhythmic, they are not absolutely so, since they are not a constant repetition of the same movement. Furthermore, there is also an underlying slow, sinuous type of movement. Lastly there is a typical choreiform or athetoid posture of the hand.

Dr. E. Sachs and Dr. Putnam spoke of the use of barbiturates in this case and of their effect. The dose used was enormous as compared with that usually given. The patient was given 7½ grains (0.486 Gm.) of pentobarbital sodium and 2 grains (0.13 Gm.) of soluble phenobarbital (sodium phenobarbital), sufficient to put him to sleep and to keep him asleep for some time. The picture showing abolition of all involuntary movements by these drugs was taken twenty-four hours after their administration. I doubt whether these drugs in the dosage required can serve any useful therapeutic purpose. I have used them only experimentally. The patient shown here was one of three to whom large doses of barbiturates have been given, resulting in an abolition of the involuntary athetoid movements. It was interesting to learn that Dr. Putnam has had a different experience with tribromethanol in amylene hydrate. It must be that the action of the two is quite different and on different portions of the central nervous system.

Dr. E. Sachs and Dr. Fulton have discussed the area which has been extirpated. In his case Dr. Sachs removed the entire precentral gyrus in the area controlling the movements of the arm and thus extirpated both area 4 and area 6 at that level. In my cases I have attempted to preserve the caudal part of the precentral gyrus in which the Betz cells are located. But unlike Dr. Sachs, I carried the extirpation down into the lateral ventricle in this particular case. In spite of my efforts to spare the Betz cells and the pyramidal tract, there can be no question but that they, as well as the parapyramidal fibers from area 4 must have been damaged. The extent of the damage to the pyramidal tract cannot be determined, as it was severely damaged by the disease process prior to operation. In the most recent case of this type the extirpation was limited to the cortex, as was done in Dr. Sachs' case, and the results have been comparable to those shown here. Even here I feel certain that although area 4 was not removed, the Betz cells cannot be said to have entirely escaped being damaged both by the immediate trauma and by the subsequent scar formation.

DR. E. SACHS, St. Louis: You take out more in front than I do, do you not?

DR. P. C. BUCY, Chicago: Yes, I remove the caudal part of the second frontal convolution and even part of the first in order to be sure of removing all of area 6 in the area controlling the arm.

Dr. Putnam raised the question as to whether he is interrupting the same fiber systems in his operation on the spinal cord that I interrupt by removing the

cerebral cortex. I doubt whether Dr. Putnam is sectioning the axons of the neurons, the cell bodies of which I remove. He may, however, be interrupting the second or third neuron in the same nervous pathway. There arise from this precentral region a great variety of fiber tracts. Except for the pyramidal tract none descends to the spinal cord. The other extrapyramidal or parapyramidal fibers descend to subcortical centers, such as the substantia nigra and the pontile nuclei. Which of the various fiber tracts in the parapyramidal system is concerned in the production of these involuntary movements is unknown.

Dr. Putnam has also raised the question as to what conditions are suitable for this procedure of cortical excision. I have utilized this procedure only in cases in which the involuntary movements are entirely or predominantly unilateral. In all of my cases the extremity has been further incapacitated by hemiparesis. In view of Dr. Sachs' experience in which a remarkable recovery of useful voluntary movement returned to the extremity after the operation, it appears that the procedure could be extended to persons with more useful extremities. I do not believe that this procedure is applicable to bilateral athetosis or generalized dystonia, for which Dr. Putnam has been performing chordotomy.

Encephalography has revealed no localized abnormality of significance in any of our cases.

Microscopic examination of the cortex removed at operation has revealed definite abnormalities in every instance. I have intentionally omitted mentioning these findings in the presentation of this patient, first, because I do not know what relation these abnormalities bear to the development of the movements and, second, because I do not wish at this time to confuse the lesion responsible for the release of these movements with the physiologic mechanism which produces the movements.

Dr. Mackay raised the question of alterations in spasticity, reflexes, voluntary movement and atrophy following operation.

Voluntary movement was not greater after operation than before, but it was definitely more useful, as it was no longer hampered by the extensive involuntary movements.

This patient, like all the others, had spastic hemiparesis on the side involved by the athetosis. After operation, except for the first few days, the spasticity, tendon and plantar reflexes were as before operation. Nor was there any change in the size of the extremity or its musculature.

Dr. Penfield has asked concerning the apparent reduction in the involuntary movements in the ipsilateral arm. There did appear to be a slight reduction in these movements immediately after operation, but this did not persist. I believe the condition of the left arm is the same now as it was before operation. The electromyographic tracings support that opinion.

Dr. Naffziger mentioned the procedure of destroying the cortex by the injection of alcohol, a procedure utilized also by Nasaroff. I was happy to learn of the improvement in one of his patients, but I do not know the explanation of his failure to obtain abolition of the movements in the other three cases. I have been more fortunate. In all three cases in which I have operated there has been a lasting improvement. In only the first case (previously reported) has there been a complete and permanent abolition of the involuntary movements. In the other two cases some involuntary movements have returned, although to nothing like the extent present before operation. It is my opinion that these results can be improved on by making a more extensive extirpation, including area 4 as well as area 6.

ANATOMIC AND PNEUMOGRAPHIC STUDIES OF THE TEMPORAL HORN

WITH A FURTHER NOTE ON PNEUMOGRAPHIC ANALYSIS OF THE CEREBRAL VENTRICLES

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AND
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In published pneumographic ventricular studies the temporal or inferior horn of the lateral cerebral ventricle has received scant attention, and there is a persisting misconception of its shape to be found in textbooks of anatomy. The supracornual cleft and the body of this horn frequently appear as separable shadows in pneumograms, as will be described, and undergo typical changes in pathologic states.

We are taking this opportunity also to describe a method of ventricular analysis which we have found helpful for use as a routine. In this analysis the ventricular subdivisions proposed by Torkildsen and Penfield [1] are used. These subdivisions are made up of those portions of the lateral ventricle which appear as separable shadow outlines on an anteroposterior roentgenogram. This may be understood by reference to figure 1, in which the view with the *brow up* should be compared with the left lateral view (*L. L. V.*), or by use of the Torkildsen ventricular model,[2] on which the subdivisions are marked.

ANATOMIC FEATURES

The hippocampus major, or cornu ammonis, is a curved eminence which forms the floor of the temporal horn of the lateral ventricle through its entire length of about 5 cm. (fig. 2 *A* and *B*). Its lower

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From the Montreal Neurological Institute.

Read by title at the Sixty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 3, 1936.

The words "pathologic" and "neurologic" are used in order to conform to the terminology which is compulsory for publication in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. The authors would prefer to use the words "pathological," "neurological," etc.

1. Torkildsen, A., and Penfield, W.: Ventriculographic Interpretation, Arch. Neurol. & Psychiat. **30**:1011 (Nov.) 1933.

2. Made by the George P. Pilling & Son Company, Philadelphia (Torkildsen, A.: An Analysis of Shadows Seen in Pneumograms of Cerebral Ventricles, Acta psychiat. et neurol. **9**:465, 1934; Gross Anatomy of Lateral Ventricles, J. Anat. **68**:480 [July] 1934).

end is enlarged and presents two or three round elevations and is consequently named the pes hippocampi. On section the hippocampus is seen to be formed by the inward folding of the wall of the hemisphere in the hippocampal fissure.

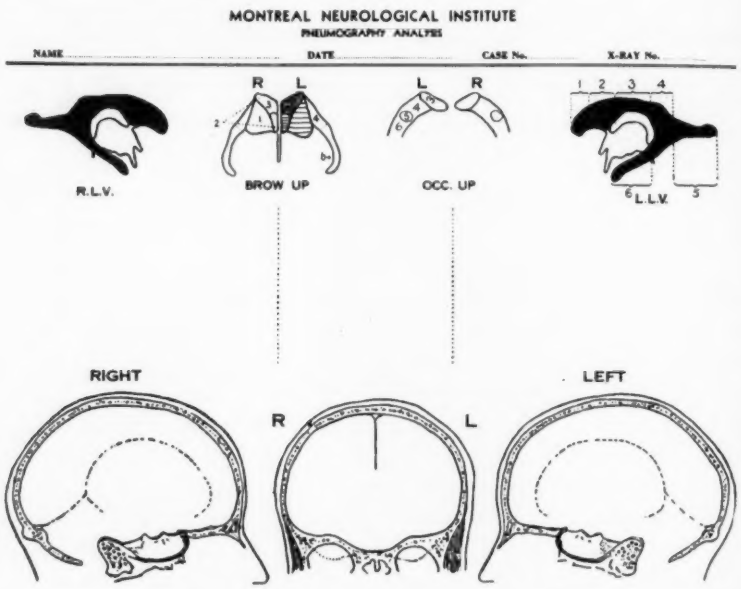

Fig. 1.—Form used for routine analysis of ventriculograms, modified after McConnell and Childe [4] and Torkildsen and Penfield.[1] The view labeled *Brow up* shows the portions of the lateral ventricle seen as unit shadows in that view. The same units are indicated in the lateral view *L. L. V.* For any individual case, the actual pneumographic shadows are traced from the roentgen film onto the space below each of the four corresponding views, as shown in figure 11 and subsequent similar charts. The lesion is then drawn into its position in the cranial diagrams at the bottom of the figure.

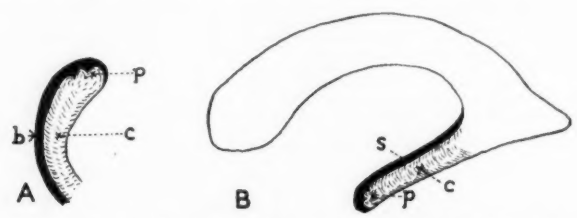

Fig. 2.—Diagrams of the temporal horn opened (*A*) from above and (*B*) from its lateral aspect. In this figure, *b* indicates the body of the temporal horn; *c*, the cornu ammonis or hippocampus; *p*, the pes hippocampi, and *s*, the supracornual cleft.

The inferior horn of the ventricle, which tunnels the temporal lobe to within about 2.5 cm. of its tip, lies in the mesial portion of this lobe.

The horn folds over the hippocampus, covering it above and laterally throughout its full extent. Thus, the ventricular horn, if cut across in a frontal section at almost any point, is crescentic, the concavity being inward and downward. At the inferior tip the ventricular horn passes over the pes hippocampi and just beyond it, to terminate by turning sharply mesially and downward.

Thus, that portion of the inferior horn which is lateral to the cornu ammonis, occupying a vertical plane, we propose to call the body, and that portion which is above the cornu ammonis, occupying roughly a horizontal plane, we would call the supracornual cleft. It would seem expedient to make this subdivision, for in pneumograms with complete filling these two portions may be sharply differentiated and either may

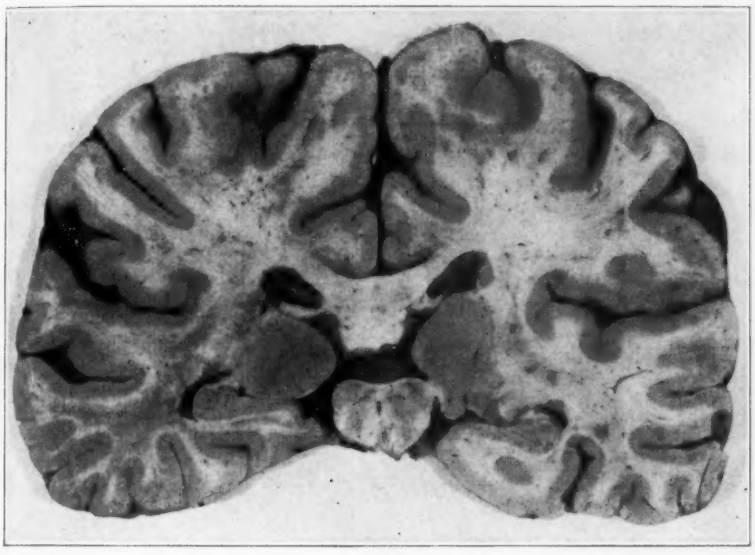

Fig. 3.—Section through the normal temporal horn, showing the body and the supracornual cleft, produced by the bulging hippocampus.

be filled with gas while the other still contains fluid. Furthermore, in some instances these two portions are separated anatomically, as will be described.

In the normal temporal lobe this wrapping of the temporal horn about the hippocampus is evident (fig. 3). The supracornual cleft contains the choroid plexus all the way to the tip of the horn, for the plexus is attached to its mesial wall. Sections through a moderately dilated ventricle show that the temporal horn is more rounded as well as larger, and that the projection formed by the hippocampus is relatively smaller in comparison with the ventricle (fig. 4). However, the same portions

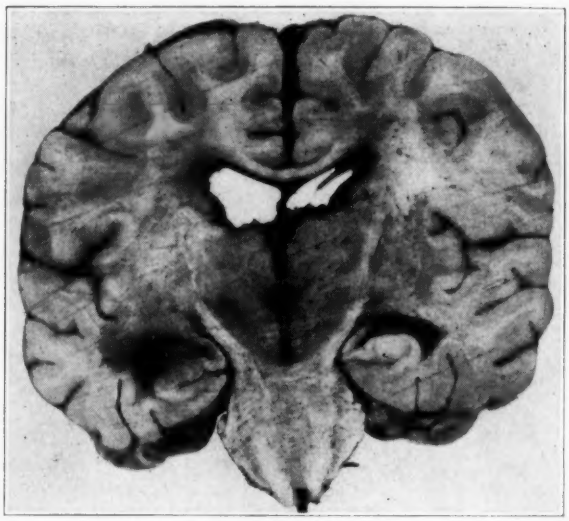

Fig. 4.—Section through a moderately dilated temporal horn, illustrating that the hippocampus still bulges into the ventricle but is relatively smaller.

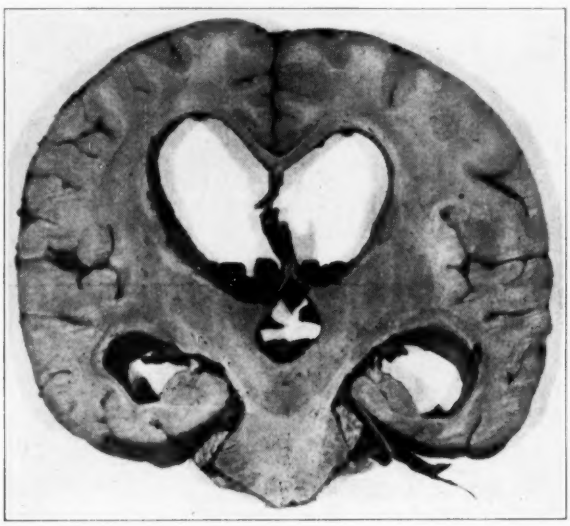

Fig. 5.—Section through a hugely dilated temporal horn, showing the slight prominence of the hippocampus.

are still separable. Sections through a hugely dilated ventricle show that the hippocampus still forms a slight prominence in the medial wall of the temporal horn (fig. 5) but that it now has become quite unimportant in relation to the large ventricular cavity.

We recently sectioned a brain in which the supracornual cleft and the body of the temporal horn on one side formed two portions, separated from each other by a strip of white matter (fig. 6). In this case the two portions were connected anteriorly and posteriorly. The choroid plexus lay within the separated supracornual cleft.

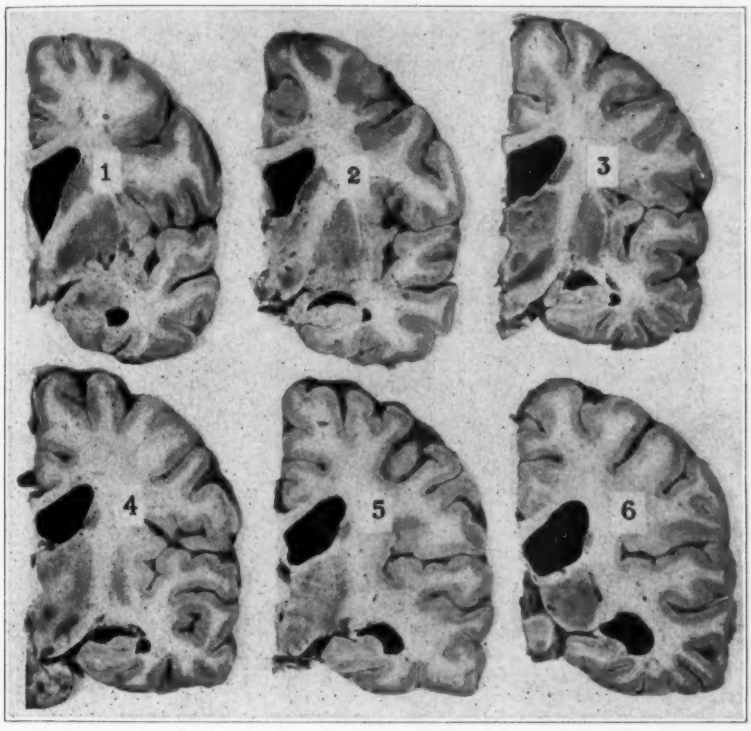

Fig. 6.—Serial frontal sections through a hemisphere, numbered *1* to *6* from before backward. The body and the supracornual cleft of the inferior horn are separated, as may be seen in slabs *2* to *4*.

PNEUMOGRAMS

When there is general ventricular dilatation and sufficient gas is present, the temporal horn is readily recognized [3] in lateral pneumograms taken with the patient lying down (fig. 7). It appears as a

3. The temporal horn can rarely be shown with the patient erect, as it then forms the lowest point of the lateral ventricle and consequently contains cerebrospinal fluid.

round structure, not unlike the diagrams shown in textbooks. As the roentgen beam passes through a thick layer of gas, the shadow is uniform in density.

The appearance is quite different when dilatation is not present. Unless the head is postured carefully, the temporal horn may not be shown at all in lateral films. If it is successfully filled with gas, stereoscopic examination is essential both to lateralize the ventricle and to demonstrate sharply its size and shape. The body of the normal temporal horn is usually quite faintly outlined, as the rays pass through a layer of gas frequently only 1 or 2 mm. in thickness. On the other

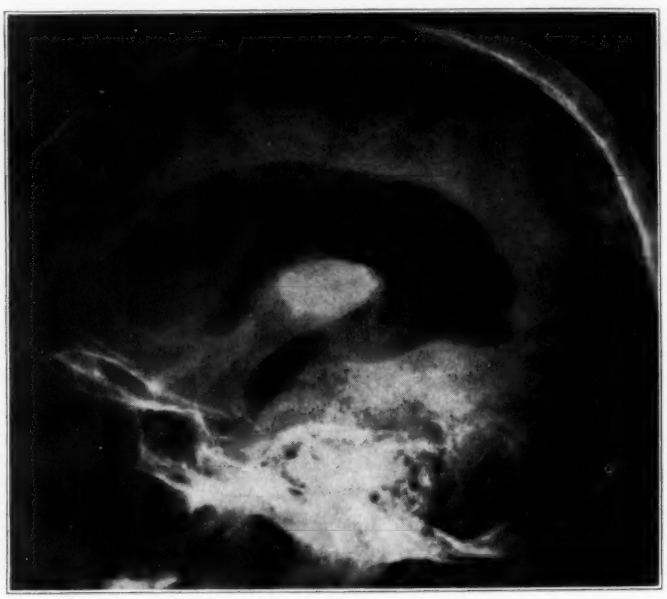

Fig. 7.—Lateral appearance of the temporal horn, when general ventricular dilatation is present.

hand, the supracornual cleft, having its width parallel to the beam, casts a comparatively dense, though narrow, shadow. This is illustrated in figure 8.

Similarly, the tip of the horn is represented on the lateral film by a downward curving, dense shadow, because the supracornual cleft curves over the pes hippocampi (fig. 9*A*) and the body curves medially.

The recognition of these features is of practical value, as well as of academic interest. Not infrequently, the body of the temporal horn is quite indistinct or invisible, owing either to its shallow depth or to incomplete drainage. In some of these cases the supracornual cleft shows plainly, and the appearance may be mistaken for deformity pro-

duced by an expanding lesion situated below the temporal lobe (fig. 9 *B*). On other occasions, small quantities of gas may be trapped in the lower of the two temporal horns, in which case the gas fills the supracornual cleft. This also throws on the film the narrow, dense shadow of the cleft, without the wide, faint shadow of the body.

Gas is trapped in the temporal horn comparatively frequently when anteroposterior films (with the brow up) are made. It then outlines the tip of the horn. As seen in this view, the tip lies about halfway between the midline and the surface of the skull (fig. 10). The posterior portion of the temporal horn may be moderately well shown in films made with the occiput up, but usually the terminal portion contains fluid in this position and is not visible.

PATHOLOGIC DISTORTION

With proper understanding of the anatomic features of the temporal horn distortions are more easily appreciated, whether they are due to

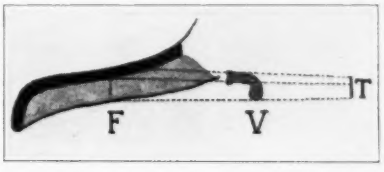

Fig. 8.—Diagram illustrating production of shadows of different density on the roentgen film in the normal and in the moderately dilated temporal horn, as visualized in lateral roentgenograms. The ray leaves the tube (*T*), passes through the inferior horn, as indicated by its frontal section (*V*), and casts shadows on the film (*F*).

compression by an expanding lesion within the skull, to ventricular distention, to focal cerebral atrophy or to cicatricial contraction. The other portions of the ventricles must be considered as well, especially the third ventricle. In this regard, we find it useful to express graphically the distortions of all parts of the ventricles simultaneously by means of the composite chart described by McConnell and Childe [4] and now modified as indicated in figure 11 and subsequent similar charts.

Expanding lesions within the middle cranial fossa produce a variety of alterations in the shape and position of the horn. In our experience obliteration is extremely rare. This is in direct contrast to some published statements. When the head is properly rotated, so that gas is

4. McConnell, L. H., and Childe, A. E.: Pneumographic Localization of Tumors of the Brain: I. Tumors of the Lobes of the Cerebrum, Arch. Neurol. & Psychiat. **37**:33 (Jan.) 1937; II. Tumors Involving the Basal Ganglia, Lateral Ventricles, Brain Stem and Cerebellum, ibid. **37**:56 (Jan.) 1937.

allowed to ascend to the desired region, much accurate information is gained. Even with a near-by huge expanding lesion, the horn can usually be defined, both in lateral views and by means of trapped gas

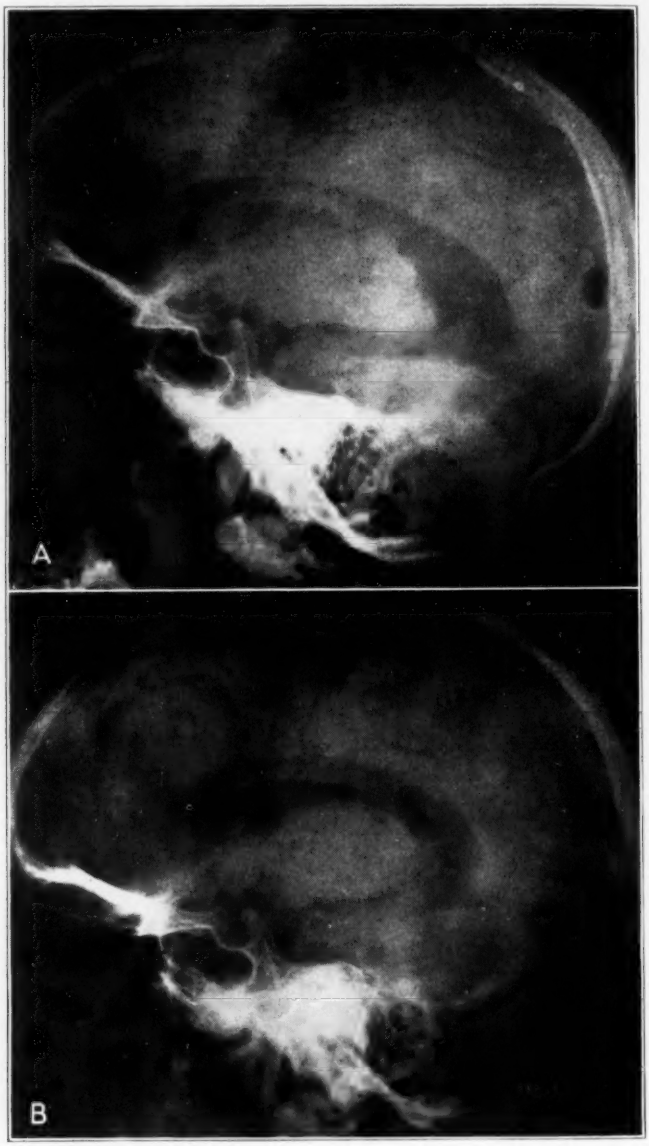

Fig. 9.—Lateral roentgenograms of the normal temporal horn, showing (*A*) the body and the supracornual cleft near the tip of the horn only and (*B*) the supracornual cleft, and not the body.

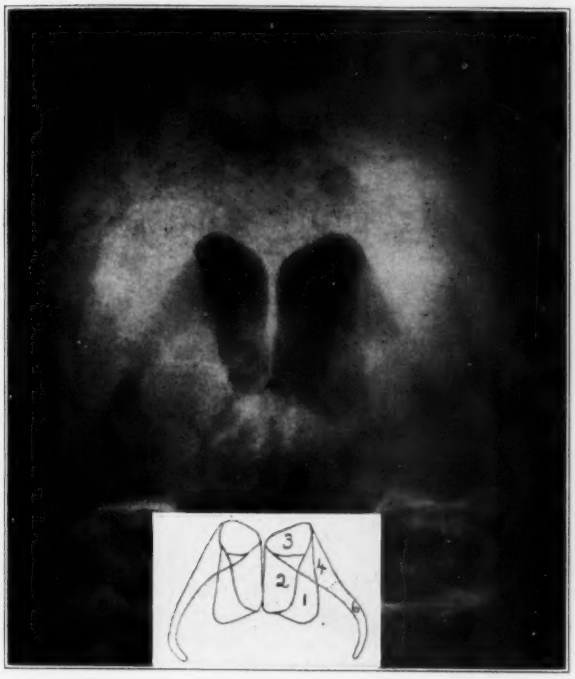

Fig. 10.—Anteroposterior film showing the entire temporal horn on both sides as well as the remaining units of the lateral ventricles, except portion 5 (fig. 1).

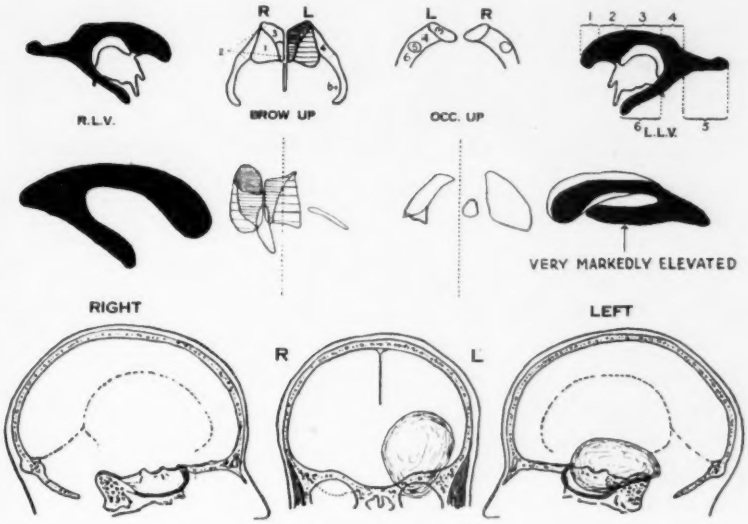

Fig. 11.—Pneumographic analysis of a tumor of the left temporal lobe, which is elevating the temporal horn markedly.

in anteroposterior views. This continuing patency is probably due to the presence of choroid plexus all the way to the tip of the horn. The formation here of cerebrospinal fluid would thus prevent collapse due to any proximal pressure. If the horn is not shown another attempt should be made to fill this portion of the ventricular system.

Definite elevation suggests, of course, a lesion situated inferiorly (figs. 11 and 12). True depression is rare but, when present, indicates a lesion situated above it. Narrowing by compression is much more

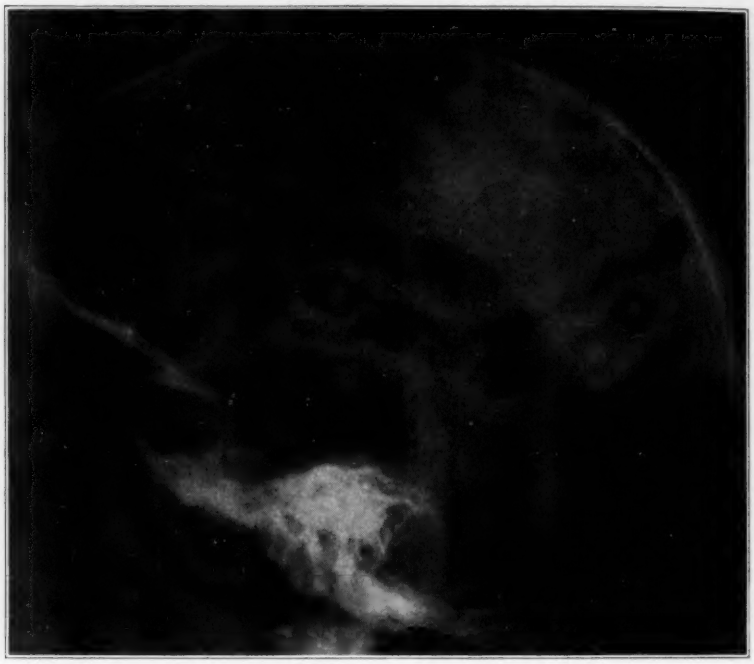

Fig. 12.—Original roentgenogram from which a portion of the tracing shown in figure 11 was made.

common but does not necessarily indicate a temporal lesion, as it is often caused by distant pressure from the parietal or the frontal lobe (fig. 13).

The postero-anterior view (with the occiput up) may be helpful, but it is usually unreliable. On the other hand, the anteroposterior view (with the brow up) may show mesial or lateral displacement of the terminal portion of the horn (figs. 14 and 15). A tumor of the insula may cut off the anterior portion of the temporal horn (fig. 16).

It is a striking feature, however, that even a large expanding lesion adjacent to the inferior horn usually fails to obliterate this fluid-filled

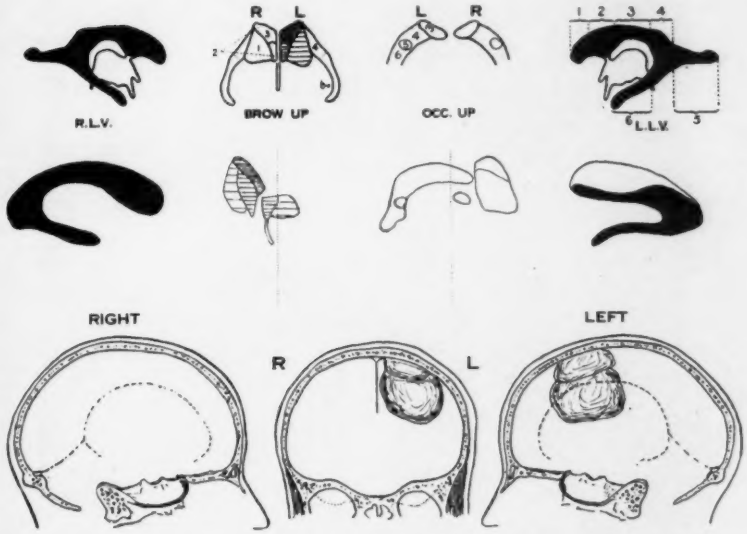

Fig. 13.—Narrowing by distant pressure on the left temporal horn, due to a tumor of the left frontal lobe.

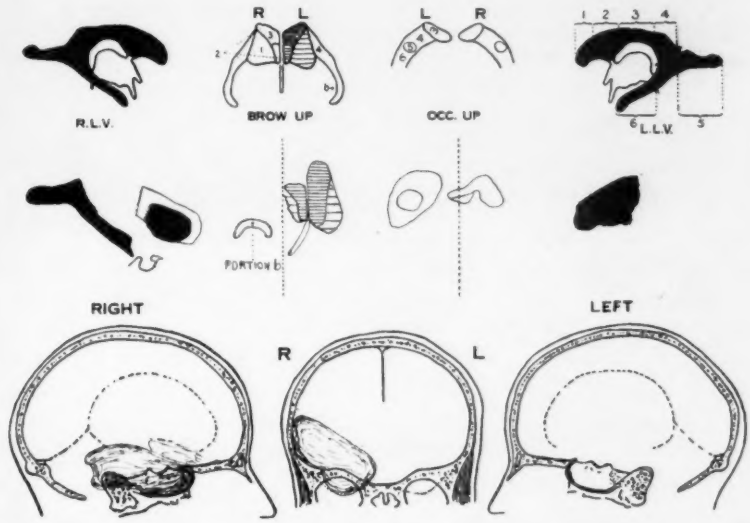

Fig. 14.—Medial displacement of the temporal horn produced by a tumor situated well lateral in the temporal lobe. A roentgenogram in the same case is shown in figure 15.

Fig. 15.—Reproduction of the anteroposterior roentgenogram used in the pneumographic analysis shown in figure 14.

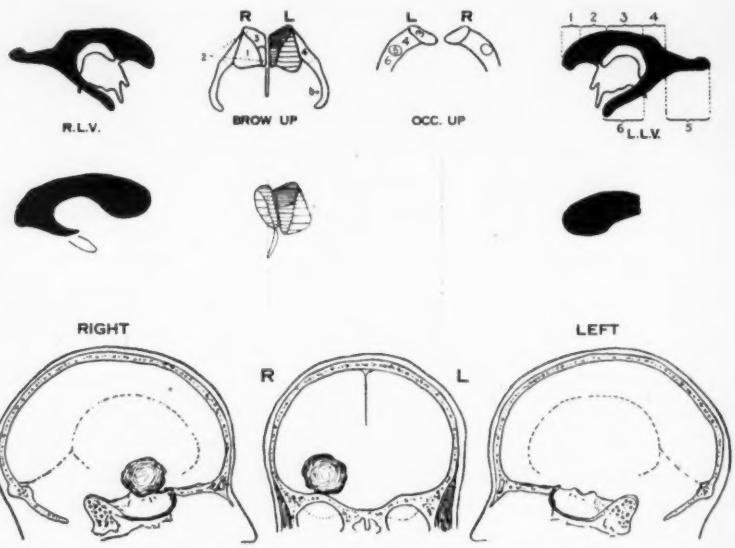

Fig. 16.—Obliteration of the terminal portion of the temporal horn by a tumor of the insula. The contralateral horn is outlined, in contrast to the ipsilateral horn.

cavity, in contrast to a lesion in the occipital or the frontal horn, which is easily obliterated. The persistence of the temporal horn is due, no doubt, to the fact that the choroid plexus is present right into the tip, and if pressure is exerted on the body of the horn, the space is held open by fluid formed under pressure by the plexus distal to that pressure.

It should be remembered that even when an expanding lesion is not placed high in the cranial cavity, the body and the anterior horn of the lateral ventricle on the same side may be depressed because of the fact that the brain about the ventricle must pass downward under the falx before it can escape into the opposite side of the skull. This may be true even with a tumor of the middle fossa; that is, a tumor of

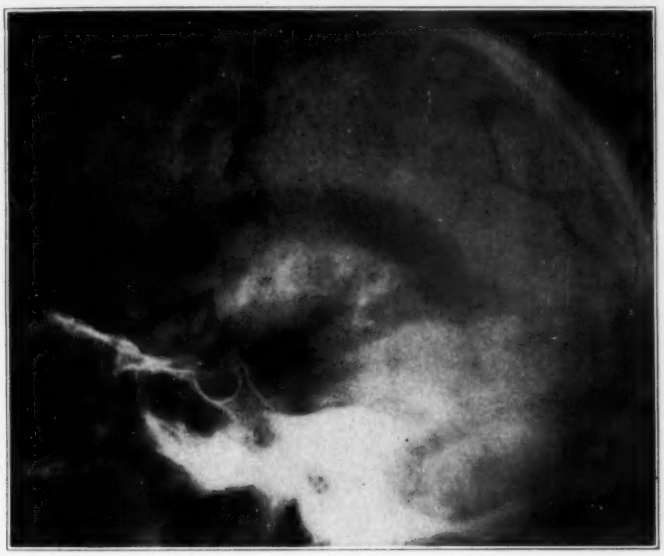

Fig. 17.—Localized dilatation of the temporal horn in a case of posttraumatic epilepsy, due to an atrophic process in the temporal lobe.

this fossa on the right side may cause a downward displacement of the lateral ventricle on that side, as well as displacement to the left (fig. 14).

Localized enlargement of the temporal horn may be easily detected with proper filling. Such enlargement may be the end-result of trauma to the temporal lobe or, in short, of any localized destructive process, such as is frequently associated with focal epilepsy (fig. 17).

SUMMARY

The outline of the temporal or inferior horn of the lateral ventricle as shown in reconstructions in most textbooks of anatomy is quite inac-

curate and does not correspond with either the cut sections of the brain or the appearance of the horn as seen in pneumograms. In most reported pneumographic studies this portion of the ventricle has been ignored.

The normal temporal horn is comparatively small and crescentic and consists of two united portions situated almost at right angles to one another, the body lying in a roughly vertical plane, lateral to the cornu ammonis, and the supracornual cleft above it, in a roughly horizontal plane.

The encephalographic form used in figure 1 is recommended for the routine analysis of abnormal conditions. The ventricular shadows are drawn by the roentgenologist. The lesion is later sketched into the diagrams of the skull on the lowest line by the clinician.

An expanding lesion of the temporal region, even when large, frequently does not obliterate the temporal horn, and the local deformities and displacements may indicate precisely the position of such a lesion. Expanding lesions of the frontal and the parietal lobe and even of the insula and the temporal lobe itself are likely to cause narrowing and displacement of the temporal horn without collapse.

Localized enlargement of the temporal horn indicates focal atrophy of the temporal lobe. The enlargement of this horn, which is associated with hydrocephalus of the whole ventricle, causes the hippocampus to make less of an imprint on the ventricle, so that the supracornual cleft can no longer be distinguished from the body of the temporal horn.

SERUM DISEASE OF THE NERVOUS SYSTEM

REPORT OF THREE CASES

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AND

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NEW YORK

The ill effects on the nervous system of the use of foreign serums injected for therapeutic purposes have been recognized since the early years of the century, the first case having been reported in 1908 by Gardère and Gangolphe.[1] Since then it has slowly become evident that the meninges, the brain, the spinal cord, the spinal roots and the peripheral nerves, both cranial and spinal, may be the site of more or less severe disease, producing a variety of syndromes, which as a rule subside, leaving few if any residua. Both the somatic and the visceral nervous system are affected. The clinical pictures, the pathologic basis and the questions of etiology and prognosis have gradually been clarified.

Reports of cases have accumulated in the United States, France, England, Belgium, Switzerland, Germany, Italy and Czechoslovakia. The greatest number are from France, no doubt stimulated by the report of three cases in 1919 by Lhermitte.[2]

General reviews of the subject have appeared in the French, English and American literature during the last fifteen years. The reviews in English are that of Allen,[3] in England, in 1931, that of Doyle,[4] in the United States, in 1933. The first case reported in England was that of Dyke,[5] in 1918, while in the United States Kennedy [6] first drew attention to the subject in general in 1929, though a report of cases of optic

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Read at the Sixty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 1, 1936.

1. Gangolphe: Névrite au cours d'un cas de tétanos traité par la sérotherapie, Lyon méd. **110**:497-499, 1908.

2. Lhermitte, J.: Les paralysies amyotrophiques dissociées du plexus brachial à type supérieur consécutives à la sérothérapie antitétanique, Gaz. d'hôp. **92**:1053-1056, 1919.

3. Allen, I. M.: The Neurological Complications of Serum Treatment, with Report of a Case, Lancet **2**:1128-1131, 1931.

4. Doyle, J. B.: Neurological Complications of Serum Sickness, Am. J. M. Sc. **185**:484-492, 1933.

5. Dyke, S. C.: Peripheral Nerve Lesions After Antitetanic Serum, Lancet **1**:570, 1918.

6. Kennedy, Foster: Certain Nervous Complications Following Use of Therapeutic and Prophylactic Sera, Am. J. M. Sc. **177**:555-559, 1929.

neuritis by Mason [7] had appeared in 1922. Roger and Poursines [8] reviewed the literature in 1932. Vogel [9] reviewed the cases from the German literature in 1935; he recorded eight and noted that the first of these was reported as recently as 1927.

Ten theses of French origin have appeared since 1920, the most recent being that of Pessin,[10] in 1933.

The first mention of this relatively rare neurologic disorder which has been found in a textbook or system of medicine and neurology was that of Tinel,[11] in 1927. Longcope,[12] Mackenzie,[13] Wechsler,[14] Moser [15] and Brody [16] gave more or less detailed accounts. This brief historical review shows how relatively recent is knowledge of the allergic neurologic disorders due to serum sickness.

Other diseases of the nervous system, such as angioneurotic edema, epilepsy, migraine and headache, have been regarded as due in some cases to allergic intoxication by substances other than serums. Kennedy [17] laid special emphasis on such conditions. Possibly related to the general subject are those comparatively rare cases of sudden death due to allergy. Involvement of the vital centers of the nervous system may be at fault. The question is still to be answered.

However interesting it would be to consider the general subject of allergic disease of the nervous system, the present report will be limited to the condition due to serum sickness.

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7. Mason, V. R.: Optic Neuritis in Serum Sickness, J. A. M. A. **78**:88-89 (Jan. 14) 1922.

8. Roger, Henri, and Poursines, Yvres: Les formes polynévritiques des paralysies sérothérapiques, Arch. de méd. gén. et coloniale **1**:65-78, 1932.

9. Vogel, P.: Ueber Polyneuritis nach Seruminjektion, Nervenarzt **8**:11-17, 1935.

10. Pessin, David: Les paralysies postsérothérapiques; état de la question, Paris, Jouve & Cie, 1933.

11. Tinel, J., in Roger, G. E. H.; Widal, F., and Teissier, P. J.: Nouveau traité de médecine et de thérapeutique, Paris, Masson & Cie, 1927, vol. 21, pp. 353-355.

12. Longcope, Warfield T.: Serum Disease, in Nelson Loose Leaf Medicine, New York, Thomas Nelson & Sons, 1932, vol. 2, chap. 4.

13. Mackenzie, G. M.: Serum Disease and Serum Accidents, in Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1933.

14. Wechsler, Israel S.: A Textbook of Clinical Neurology, with an Introduction to the History of Neurology, ed. 3, Philadelphia, W. B. Saunders Company, 1935.

15. Moser, K., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 9, pp. 936-939.

16. Brody, S. B.: Serum Sickness, in Blumer, G.: The Practitioners Library of Medicine and Surgery: Neurology and Psychiatry, New York, D. Appleton-Century Company, 1936, vol. 9, pp. 409-410.

17. Kennedy, Foster: Allergic Manifestations in the Nervous System, New York State J. Med. **36**:469-474, 1936; footnote 6.

ETIOLOGY

It has been recognized for some years that the cause of the disorder in question is an allergic or anaphylactic reaction in the body due to a foreign serum and that the specific antitoxins in the serum play no part. Thus, identical pictures have resulted from the administration of serums used to prevent or to treat tetanus, diphtheria, scarlet fever, tuberculosis, gangrene infection and infections with the pneumococcus, gonococcus, meningococcus and streptococcus. The administration of horse serum has also produced the condition. Disorders following the use of vaccines are not included in this report.

In the greatest number of cases the condition has followed the administration of antitetanus serum. The relative rarity of cases in which it has followed the use of diphtheria antitoxin has been thought to be due to the youth of the patients receiving it, for in general children are relatively immune to serum sickness and diphtheria antitoxin is given most often to young patients.

As to age incidence, the disorder occurs predominantly in persons over 21. Males are more often affected than females, probably owing to the relatively greater frequency of accidents among males, with the consequent more frequent use of antitetanus serum.

PATHOLOGIC CHANGES

The combined evidence from cases in which autopsy has been performed, several experimental studies, the findings in the cerebrospinal fluid in cases of serum disease not complicated by outspoken neurologic syndromes and several cases in which such syndromes were shown indicates the nature of the pathologic process. For purposes of criticism, it is important to bear in mind the two theories of serum disease. One regards the blood vessels as the primary site of the disease; the other, the cells.

The most recent experimental work was that of Garcin and Bertrand.[18] With repeated anaphylactic shocks produced in animals with foreign serums there was resulting perivascular infiltration, cellular destruction in the nervous system and meningeal reaction with lymphocytes. Stief and Tokay[19] approached the problem in the same way,

18. Garcin, R., and Bertrand, I. Y.: Etude expérimentale des lésions du névraxe consécutives aux chocs anaphylactiques répétés et aux injections réitératives espacées d'albumine étrangère. Sur quelques considérations pathogéniques applicables à la neuro-pathologie humaine, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:787-796 (May 13) 1935.

19. Stief, A., and Tokay, L.: Durch experimentelle Serumanaphylaxie verursachte veränderungen des Nervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:715-728, 1934.

by producing repeated anaphylactic shocks, and obtained two groups of results. In one, dilatation of blood vessels predominated, and in the other, parenchymal changes consisting of cell degeneration, with disappearance of the Nissl bodies. These changes were observed in such nuclei as the olive and the facial nucleus. In dogs they were also present in the cortex. No glial overgrowth was seen. Stief and Tokay questioned whether the changes in the cells were secondary to those in the blood vessels. They also called attention to the two theories of the site of anaphylactic reactions but did not attempt to reach a final conclusion as to their relations or correctness. They regarded the occurrence of spontaneous meningitis and meningo-encephalitis in one rabbit as insufficient experimental evidence of this kind of reaction to anaphylactic shock. Dechaume and Croizat,[20] basing their conclusions on experimental work and clinical evidence, described the presence of vasocongestion and at times minute hemorrhages. They expressed the belief that these lesions, if extensive enough, would cause the destruction of neighboring nerve tissue. This, then, they suggested as a cause of sudden death, if vital parts of the brain were affected.

This experimental work was supported by the postmortem observations of Roger, Poursines and Recordier,[21] in which enormous dilatation of the ventricles and increase of cerebrospinal fluid were evident grossly. Microscopic examination showed vasodilatation, perivascular edema and small hemorrhages, without any glial overgrowth, in both the brain and the spinal cord. The meninges showed the same type of dilated blood vessels and greatly widened spaces, indicating increase of the cerebrospinal fluid. Occasional degenerated cells, with loss of Nissl bodies and areas of necrosis, were observed in the central nervous system. Neuronophagia was absent. In the spinal roots and nerves interstitial radiculitis and neuritis were present. Winkelman and Gotten [22] reported one case in which postmortem examination was made. They noted glial and lymphocytic infiltration of the spinal cord, the brain and the meninges, with necrotic areas in the parenchyma of the nervous system. Clinically the condition in this case was a combination of a cerebral syndrome, with choked disk and jargon aphasia, and ascending sensorimotor paralysis.

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20. Dechaume, J., and Croizat, P.: Système nerveux et anaphylaxie; faits expérimentaux; documents anatomocliniques, Paris méd. **2**:262-272 (Oct. 1) 1932.

21. Roger, H.; Poursines, Y., and Recordier, M.: Polynévrite après sérothérapie antitétanique curative, avec participation du névraxe et des méninges (observation anatomoclinique), Rev. neurol. **1**:1078-1088 (June) 1934.

22. Winkelman, N. W., and Gotten, N.: Encephalomyelitis Following Use of Serum and Vaccine: Report of Two Cases, One with Autopsy, Am. J. Syph. & Neurol. **19**:414-424, 1935.

Biopsy of specimens of muscle by Pommé and Noël [23] showed marked proliferation of the cells of the walls of the blood vessels, causing almost complete obliteration. Their observations in regard to muscle tissue and nerve endings are not convincing.

The clinical findings of increase in the amount and pressure of the cerebrospinal fluid, with a slight lymphocytic reaction, and the not infrequent edema of the retina also indicate a process of vascular origin. De Lavergne and Abel,[24] in twenty cases of serum disease in which there was no complicating neurologic syndrome such as this paper describes, demonstrated that abnormalities of a definite nature existed in the cerebrospinal fluid. They performed spinal puncture as soon as urticaria appeared and repeated the procedure until it had disappeared. They found at the beginning of the urticaria that the amount of sugar was increased. The next day the tension of the fluid was increased; lymphocytes, from 5 to 28 per cubic millimeter, were present (with rarely a few polymorphonuclear cells), and albumin was normal in amount. This picture disappeared with the urticaria. The authors related these findings to the severe headache, nausea and vomiting associated with this stage of serum disease. They found that the patients were much relieved by puncture. They regarded these changes in the cerebrospinal fluid as evidence of a neurologic disorder characterized by the symptoms mentioned. They expressed the belief that these changes were due not to infection or toxins but to the allergic disorder produced by the foreign serum.

All the findings seem closely allied to the pathologic process causing edema, swelling and vasodilatation in the skin (urticaria) and joints. It seems justifiable to conclude that the neuropathologic changes associated with serum sickness are the same as those which appear elsewhere in the body and consist of a primary disorder of the blood vessels, causing nutritive impairment of the tissues of the nervous system and interfering temporarily as a rule with the activity of the nerve fibers and cells, but occasionally causing cell death and parenchymal necrosis. A vascular disorder also produces the meningeal picture and excess of spinal fluid. An edematous process may occur in the perineural sheaths, or the nutrition of the roots or nerves may be interfered with by impairment in the blood supply, thus causing various radicular and neural syndromes.

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23. Pommé, B., and Noël, R.: Examen de biopses musculaires pratiqués au cours de l'évolution des paralysies amyotrophiques postsérothérapiques, Paris méd. **1**:532-535, 1935.

24. de Lavergne, V., and Abel, E.: Des modifications du liquide céphalo-rachidien au cours des réactions sériques, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:488-491, 1926.

GENERAL COURSE AND SPECIAL SYNDROMES

Serum sickness involving the nervous system produces a group of syndromes almost as varied and numerous as syphilis or epidemic encephalitis. Though, as has been shown in the preceding section, the nature of the pathologic process is reasonably well defined, there is still no adequate explanation of the widely different sites of involvement in the various cases reported. There is also no adequate explanation of the relative immunity to these neurologic disorders of most patients who receive serum. Heredity or previous sensitization may play a part, but a larger group of cases studied from these points of view would be required to establish these factors.

The course of the disease at its beginning is fairly constant, though no manifestations may be present until an outspoken neurologic picture appears as the first sign of trouble.

As a rule a person who is injured and is given tetanus antitoxin or who suffers from one of the infections previously mentioned and is given a therapeutic serum suddenly shows new symptoms about a week after receiving the serum. There may be moderate or high fever; urticaria, either generalized or limited to the region of the injection or to other regions, such as the face; pain; swelling and increase in temperature of one or many joints; enlargement and painfulness of the lymph nodes; severe neuralgia in one or several extremities; headache; nausea, and vomiting. The findings in the cerebrospinal fluid [24] during this early stage of serum sickness are indicative that a definite neurologic disorder in the form of meningeal irritation is responsible for several of the symptoms, e. g., headache, nausea and vomiting. The severe neuralgias also occur in this group of neurologic symptoms. According to this point of view, another syndrome is added to the more frankly neurologic syndromes to be described presently—one which precedes them and disappears before their onset, or soon after.

After the initial onset the picture varies according to the syndrome which appears. There is no relation between the site of injection and the site of the disease of the nervous system. The syndromes may be divided into: (1) cerebral, (2) spinal, (3) radicular and (4) neural.

The cerebral syndrome may be characterized by choked disk, meningeal irritation, the Kernig sign and such additional manifestations as aphasia, alexia, hemianopia and hemiplegia. The spinal fluid pressure is much increased. The cellular reaction is slight. Associated paralysis of the cranial nerves or a bulbar syndrome, with or without tetraplegia, occurs. These syndromes are cerebroneural.

The spinal, radicular and neural syndromes are usually easy to establish. On the other hand, combinations of these syndromes are also frequent, so that it may be necessary to speak of spinoradicular and

radiculoneural and even of spinoradiculoneural syndromes. Many who have reviewed the subject or reported cases have discussed the site of involvement. The general impression gained from these discussions and from the clinical reports of cases is that the allergic process may affect various combinations of the elements of the spinal cord and various combinations of the three parts of the peripheral neurons—spinal, radicular and neural. With these syndromes a cerebral form may be combined, with or without involvement of the cranial nerves.

The most characteristic picture is involvement of the Erb-Duchenne type; that is, the muscles supplied by the fifth and sixth cervical roots are affected, either unilaterally or bilaterally. Symmetrically severe involvement is usually not present, one side being more affected than the other. The patient first complains of pain in the shoulder region, radiating downward on the chest wall beneath one or both axillae. He then notices weakness in movements of the shoulder muscles, followed by complete paralysis. In a week or ten days, wasting of these muscles becomes apparent and is progressive and severe. The condition remains for from three to eighteen months, although there is progressive improvement in some muscles. In most cases the improvement leads to complete cure. In a few instances slight weakness and atrophy remain in one of the affected muscles—often the deltoid.

Cases of neural syndromes consisting of isolated involvement of the circumflex, the ulnar, the median, the radial or the external popliteal nerve or the entire sciatic nerve have been reported. One muscle, such as the serratus magnus or the deltoid muscle, may be affected. As to disturbances of the cranial nerves, optic neuritis occurs. The oculomotor nerves and the seventh, ninth, tenth and eleventh nerves may be affected, either alone or in combination with other syndromes.

A sensorimotor tetraplegic picture, with a combination of sensory disorders and weakness and paralysis of the muscles, has occurred. In some cases of this type ataxia is pronounced and the disorder has been designated as "pseudotabes."

A paraplegic variety has been reported. A purely sensory variety occurs, affecting either a single nerve or all extremities. In the latter type glove and stocking anesthesia is shown. Cases of spinal syndromes recalling multiple sclerosis and Landry's ascending paralysis have been reported, though rarely.

In two cases recurrence of symptoms occurred, recalling the similar recrudescence of disturbances in multiple sclerosis. In one of the cases the condition was that already designated as a syndrome resembling multiple sclerosis.

In view of the involvement of both the somatic and the visceral nervous system by the primary disorder of serum disease, it is of inter-

est to describe the first report of a case of disease of the adrenal glands due to serum disease by Cordier, Morenas and Delore.[25] A clinical picture of Addison's disease, beginning ten days after serum was injected, lasted more than four months, during which improvement was noted after treatment with epinephrine and extracts of adrenal gland. The ultimate outcome in the case was not given.

A form of serum disease of the meninges occurs in cases of meningococcic meningitis in which treatment with serum has been given. This, however, is a local reaction and is unlike the general reactions already described.

PROGNOSIS

As a rule recovery occurs, though months may be needed for complete cure. Occasionally paralysis and weakness, complete or partial, of one or several muscles may remain. The pain which is present at the onset usually disappears within a week.

TREATMENT

Treatment for the condition in its acute stages is the same as that for serum sickness. Such drugs as atropine and epinephrine are indicated. It is apparent from the description of cases of the cerebral type that marked edema is present. Treatment in cases of this type consists of the accepted methods of dehydration, such as restriction in the intake of fluids, drainage by repeated spinal punctures, administration of retention enemas of magnesium sulfate, intravenous injections of dextrose and large doses of caffeine. In none of the reports, however, were the results of such treatment discussed. Kennedy suggested the use of dextrose and large doses of caffeine in treatment for the cerebral variety. Massage and electrical therapy are indicated in the presence of muscular paralysis and wasting.

REPORT OF CASES

CASE 1.—E. B., a single man aged 36, on Sept. 18, 1931, was riding a horse and was thrown. He struck his left shoulder, causing a considerable wound that required stitches. Antitetanus serum was given at once. No ill results except generalized urticaria were noted, which disappeared in a few days. Eleven days later pain of a severe character began in the right shoulder. One day later the patient observed numbness of the right shoulder region and quivering and then paralysis of the muscles of the right shoulder. Two days later he noted stiffness of the left shoulder.

Physical Examination.—On October 3 no abnormalities were noted except those about the right shoulder. There was marked weakness on elevation of the arm forward or to the right. There was no atrophy, fibrillary twitching or reflex change.

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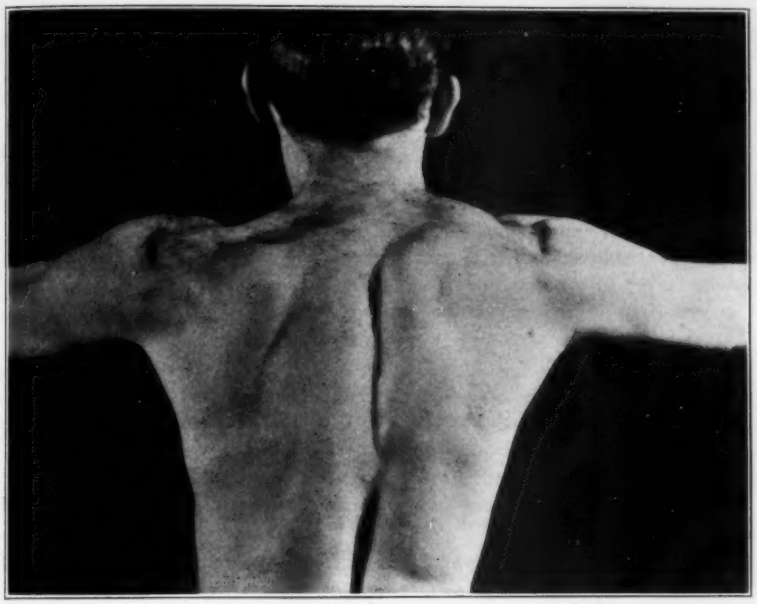
25. Cordier, Morenas, and Delore, P.: Insuffisance surrénale grave paraissant consécutive à une injection de sérum antitétanique, Lyon méd. **136**:231-233, 1925.

Course.—Two weeks later the patient showed improvement. A week after this slight atrophy appeared in the deltoid and the supraspinatus muscle on the right. In the following week the picture changed. The right arm did not improve, while the left trapezius and latissimus dorsi muscles were weak. The right deltoid and serratus magnus muscles were also weak. The right triceps jerk was diminished. Electrical tests about a week later showed only partial reaction of degeneration in the left trapezius muscle. The Wassermann reaction of the blood and the spinal fluid was negative. The spinal fluid was otherwise normal. Photographs taken periodically from October to January showed the progress of the loss of power and atrophy. The figure shows the situation on December 8, ten weeks after the first symptoms appeared. Improvement was slow, but about four months



Photograph of the patient in case 1, taken ten weeks after the first symptoms appeared.

later examination and a photograph showed practically no abnormality except extremely slight weakness of the cervical part of the left trapezius muscle. In March 1936 the condition seemed normal.

CASE 2.—J. D., a man aged 40, a widower, on Oct. 10, 1935, sustained a superficial laceration of the left hand from a nail. He received tetanus antitoxin immediately after the laceration, with no immediate ill effects. The wound in the left hand healed promptly and did not become infected. When he awoke on the morning of the seventh day after the injury, his eyes and face were swollen. He noticed itching of the scalp, although there was no rash or involvement of the joints. He had pain in the neck radiating into both shoulders and arms, which was followed in a few hours by weakness of the left shoulder and arm which, he stated, reached its maximum disability in about twenty-four hours.

Examination.—On October 31 neurologic examination gave negative results, except for the condition of the upper extremities, which included: inability to elevate either arm above the head; marked weakness of all muscles of the shoulder girdle, and pronounced weakness of the deltoid, triceps, and biceps muscles bilaterally. The motor weakness was more pronounced on the right side. There was no demonstrable motor weakness in the forearms or the hands. Reflexes: The pectoral jerks were normal on both sides; the triceps and biceps jerks were greatly reduced on the right and active on the left; the radial and ulnar reflexes were normal and equal bilaterally; the deep reflexes in the lower extremities were normal in all respects; all cutaneous reflexes were normal. The Horner syndrome was not present. The lancinating pains in the neck and the upper portion of the arms subsided somewhat after three or four days but were still present three weeks after the onset. No objective sensory changes were demonstrable except questionable slight hyperesthesia over the upper lateral aspect of both arms.

Course.—Reexamination on March 25, five months after the onset, showed decided improvement both subjectively and objectively. The patient still complained of occasional pain in the right biceps muscle. At this time he was able to elevate the left arm above the head and to execute all movements of the arm and shoulder, with slight limitation. The right arm could be abducted and extended upward only 45 degrees. On this date slight atrophy was observed in the deltoid, biceps and triceps muscles on the right side. Reexamination of the reflexes in the upper extremities showed that the triceps and biceps jerks on the right were somewhat more active than they had been at the original examination but were not as active as the reflexes on the left, which were considered normal. Sensory examination gave normal results.

Case 3.—C. J., a boy aged 12 years, on Aug. 18, 1934, cut his left foot with an ax. On the following day he received tetanus antitoxin. The wound of the foot healed without complications. On the seventh day after receiving tetanus antitoxin the boy had a rash over the entire body and stated that his scalp and body itched. On the following day, that is, eight days after administration of tetanus antitoxin, he complained of shooting pains in both arms; these pains did not disappear for one month.

Neurologic Examination.—On October 2 there were: slight atrophy of the deltoid and the supraspinatus muscle bilaterally; marked weakness of all muscles of the upper portion of both arms and of the shoulder girdles, and no demonstrable motor impairment of the forearms and hands. The deep reflexes were present but reduced. The biceps and the triceps jerk were recorded as one on each side, whereas the radial, the ulnar, the knee and the ankle jerk were recorded as three. There was a slight reduction of tactile and pain sensibility in the area of the skin conforming to the radicular distribution of the fourth and fifth cervical segment.

Course.—Reexamination on October 31 showed considerable improvement; the boy made no complaints of pain; there was marked weakness of abduction of the arm, and the arms could not be extended above the head. On December 1 the boy showed decided improvement. There was still weakness in both deltoid muscles, but the arms could be abducted and extended above the head, with difficulty. On Feb. 14, 1935, neurologic examination revealed no evidence of motor weakness. The reflexes were normal. There were no sensory changes. There was possibly slight atrophy in both deltoid muscles. The patient was able to swim, throw a ball and go through all movements, without any evidence of motor weakness. He was discharged on this date as recovered.

SUMMARY

For more than twenty-five years it has been recognized that therapeutic serums, irrespective of the disease for which they are used, may produce a number of disorders of allergic nature due to involvement of the nervous system, both central and peripheral.

If one judges from the number of cases reported as compared with the number of patients to whom serum is given, these forms of serum disease are relatively rare.

The clinical pictures include signs and symptoms due to disease of almost all parts of the nervous system, but the most frequent, serious and long-lasting syndrome is that of paralysis of the muscles supplied by the fifth and sixth cervical spinal roots.

The frequent occurrence of headache, nausea, vomiting and neuralgia in the usual and well known type of serum disease constitutes a syndrome of neurologic origin which should be included in the aforementioned, more serious syndromes. If this conclusion is accepted, a mild form of serum disease of the nervous system is frequent.

The underlying pathologic process seems to be a primary involvement of the blood vessels, such as occurs in the ordinary type of serum disease.

The serious forms of serum disease of the nervous system may last for many months, occasionally leaving permanent paralysis or paresis of one or of several muscles. However, as a rule, the prognosis is good.

Treatment for these conditions is suggested. Three new cases are reported.

CONCLUSIONS

1. Therapeutic serums may produce a great variety of forms of serum disease of the nervous system.

2. The severity of serum disease of the nervous system varies greatly. The symptoms may be mild and transitory or severe and long lasting.

3. In spite of these complications of the administration of therapeutic serums, use should be made of them when they are indicated for the prevention or cure of the specific disease for which they are intended.

DISCUSSION

DR. FOSTER KENNEDY, New York: It is difficult to add to what Dr. Kraus has said. Neurologists are now familiar, I think, with these disorders. Dr. Kraus thinks, if I understand him correctly, that flaccid palsy of the deltoid muscles is due to edema of the cervicospinal roots. That may be true in some cases, but I doubt if it is usual. I believe that the usual cause of flaccid palsy of the deltoid muscles is hydrarthrosis of the shoulder joint; the joint, being enormously swollen

and painful, induces by the great edema present compression palsy of the circumflex nerve. The joints subsequently ankylose.

I believe also that a determinant in the symptoms of these disorders must be the compactness of the tissue involved. For instance, a common result of serum intoxication or allergic edema is retrobulbar neuritis. I believe that this is due not particularly to susceptibility on the part of the optic nerve to allergy or to serum intoxication but to the extreme compactness of the tissue, whereby functional debility results from edematous compression. The same, I believe, is true of the facial nerve. Bound as it is in the bony aqueduct, it suffers more compression perhaps than parts of the brain in which edema can occur without involvement of function.

I think also that allergic conditions often cause the successive paralyses of the facial nerve that one sees in certain persons who have had three, four, five or six attacks of Bell's paralysis.

The use of serum may be dangerous in the case of persons who come from allergic families. Many instances of this can be adduced. When serum is to be given and the patient himself has no history of allergy, it is wise to inquire into the family history.

My last point is that it is strange that an epidemic of serum sickness did not occur during the Great War. I did not see any cases of serum sickness in that period. Perhaps I was unaware of them. But the phenomena are dramatic and easily seen, and all who were in the army were given antitetanic serum several times; hardly any one escaped that treatment. The lack of untoward reactions is particularly interesting in that I feel sure that anaphylactic reactions are dramatic and severe when the autonomic nervous system is keyed up by a sensitive emotional state. I believe it is possible that some of the crucifixion marks of the saints may have been due to urticarial impressions in an emotional person. I am sure that this is the shadowy borderline of which Dr. Forel spoke today. But serum sickness did not occur to any extent during the Great War; I did not see it in France. I wonder whether Dr. Kraus has any explanation to offer for this odd circumstance.

Dr. B. P. Stookey, New York: I have seen three cases of these disorders; in all the fifth and sixth cervical segmental innervation was involved on both sides. I wonder whether the localization of the lesion involving the fifth and sixth cervical groups central to the distribution of the circumflex nerve is associated in certain persons with an abnormal course or an abnormal position of the fifth and sixth roots as they leave the cervical dural sac.

In performing operations in the region of the cervical portion of the cord, I am impressed occasionally with certain anomalies of position of the fifth and sixth roots and with the fact that occasionally a nerve root apparently has little extra space as it passes through the dural opening. In the presence of such an anatomic arrangement, slight swelling might produce the signs found in some cases of this condition.

Dr. L. S. Kubie, New York: I wish to ask Dr. Kraus whether the cerebrospinal fluid has been subjected to any particular chemical or biologic examination in cases of this disorder. My reason for asking this is that it is known, since the work of Sir Thomas Lewis and others, that in patients who are subject to urticaria certain histamine-like bodies in the skin are apparently produced with great facility.

If a phenomenon akin to urticaria is being sought within the central nervous system, one should look for a substance which reacts to the tissues of the central nervous system in an analogous way—a chemical substance which in turn should find its way into the cerebrospinal fluid. Whether or not it would occur in

recognizable concentrations cannot be foretold. If such a substance could be found, it would throw additional light on this whole problem of allergic reactions in the central nervous system and also perhaps on the problem of the difference in the susceptibility of different persons to gross trauma to the nervous system.

DR. KRAUS: In reply to Dr. Kennedy's question: The first real report of cases of this disorder was made in 1919, at which time Lhermitte, of Paris, reported three cases in which a gunshot wound followed by treatment with antitetanus serum resulted in muscular paralysis. In these cases the sequence of events was the same as that in a group of cases previously reported by Henri Claude. It is apparent from a comparison of these two reports that the significance of the administration of the antitetanus serum in relation to the subsequent paralysis had not been recognized until the second report was made.

Dr. Kennedy has given a short abstract of a case in a soldier, which he observed abroad recently. The same sequence had occurred; that is, antitetanus serum had been given and paralysis had resulted, but the causal relation was not recognized until Dr. Kennedy saw the patient a number of months after the onset of the paralysis and recognized that it was due to the serum.

Dr. Stookey's explanation is interesting, particularly in view of the abnormal condition of the spinal fluid. In reply to his and to Dr. Kubie's discussion: Regardless of whether or not any paralysis is present, the amount and pressure of the spinal fluid are usually much increased. This has a definite bearing on Dr. Stookey's comments. In reply to Dr. Kubie's question, I may also refer to work mentioned in the article which was done in studying cases of anaphylactic shock in which there was no neuromuscular involvement. The spinal fluid was taken when urticaria first appeared and again after the urticaria had disappeared. It was shown in a large group of cases that the volume of the spinal fluid was always increased, that a few lymphocytes were present and that the sugar content diminished slightly, then increased and finally returned to normal as the urticarial and other reactions due to serum sickness disappeared. Thus, as I mentioned in the paper, the headaches, nausea, vomiting and neuralgia, as Dr. Kennedy has emphasized, are often extremely severe and are almost surely evidences of neurologic involvement associated with increase of cerebrospinal fluid, which is not as a rule recognized.

NATURE AND SIGNIFICANCE OF MULTIPLE PETECHIAL HEMORRHAGES ASSOCIATED WITH TRAUMA OF THE BRAIN

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The nature and effects of injury to the brain have been the subject of investigation since earliest recorded medical history. Gross injuries of the brain and their effects are fairly well understood, but the effects of concussion, or indeed, the cause of unconsciousness, are less well known and are still the subject of discussion and controversy, which occupy the attention of the clinician and the pathologist.

REVIEW OF THE LITERATURE

The literature on concussion up to recent years has been well covered in the important article of Jakob,[1] who repeated the classic experiment of Schmaus [2] on the spinal cord of the rabbit and extended the experiments to concussion of the brain. Schmaus reported four observations on the human subject in which concussion of the spinal cord produced a direct specific action on the primary tissues of the nervous system. In order to study further the effects of concussion Schmaus experimented with fourteen rabbits and with guinea-pigs by holding the animal vertically in the air and placing on its back a board 2 cm. thick, which was struck

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1. Jakob, Alfons: Experimentelle Untersuchungen über die traumatischen Schädigungen des Zentralnervensystems (mit besonderer Berücksichtigung der Commotio cerebri und Kommotionsneurose), in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, Gustav Fischer, 1913, vol. 5, p. 182.

2. Schmaus, Hans: Beiträge sur pathologischen Anatomie der Rückenmarkserschütterung, Virchows Arch. f. path. Anat. **122**:470, 1890.

with a hammer one or more times. The results varied with different animals. Guinea-pigs died quickly or, at the latest, on the day following the procedure, but rabbits under the same experimental conditions invariably lived longer. The older animals required from ten to fifteen such concussions for an effect; the most desirable age for rabbits was from 5 to 8 weeks. Animals of this age showed a relatively quick oncoming and persisting paralysis. As a rule, from eight to fifteen concussions were necessary, which resulted in spasm of the lower extremities but not of the upper, and this was followed by paresis of the hindlegs. The concussions were continued until the paresis was persistent; this required only a small number of subsequent concussions. If the animal apparently recovered, a smaller number of concussions caused recurrence of the paralysis. The experiments on the animals lasted from two to forty-four days. In the longest experiment, on a highly resistant animal, the concussions were repeated on the following days: the first, second, third, fourth, fifth, sixth, seventh, thirteenth, twentieth, twenty-third, twenty-seventh, twenty-eighth, thirty-first, thirty-third and thirty-fourth. No explanation was offered of why a single severe concussion has consequences in man which are produced in animals only by repeated concussions. It was suggested that the general body build and the ease with which the vibrations are transmitted from the spine to the spinal cord are variable factors.

From the results of these experiments Schmaus expressed the belief that concussion is more than a shock to the spinal cord. In cases of severe concussion necrosis of fibers takes place. He stated that more fibers are destroyed than one is able to recognize by current pathologic methods. The anatomic changes in cases of concussion may be: (1) simple degeneration of nerve elements resulting in tract degeneration; (2) necrosis resulting in softening and cavity formation and (3) gliosis and syringomyelia. The histologic picture is that of swelling and degeneration, that is, necrosis, of the axis-cylinders as the primary effect, and this was assumed to be a molecular change because of the absence of changes associated with fresh concussion. All ganglion cells in the anterior horn showed granular changes and reacted poorly to the Nissl stain. Definite degeneration of the ganglion cells was observed, however, in only one case. Schmaus referred to the appearance of the ganglion cells in cases of edema, and from his study of the preparations used as a control, he came to the conclusion that, because of defective knowledge of the behavior of these cells, great weight could not be laid on the cell changes noted.

In discussing the condition of the blood vessels Schmaus recorded only two cases of capillary hemorrhage—one in an animal two days after trauma and another (experiment 7) in which he observed two

areas of hemorrhage, one in the cervical region and one in the gray matter of the dorsal region of the cord. Fiber degeneration could not be referred to the small hemorrhages, for if this were the cause, the degeneration would not have been in the situation in which it was observed.

The vessels themselves showed no definite changes. The occasional presence of disease or defect of the vessels must also be considered accidental or secondary. In addition to the changes in the axis-cylinders and the ganglion cells, Schmaus described in detail a homogeneous mass in the gray substance, corresponding to that observed in a human subject (observation 2). The conclusion was reached that it could be due only to conversion products of degenerated glia. The accompanying capillary hemorrhages were regarded as only secondary. The substance was poor in cells; there were some epithelioid and round cells, and the vessels were not thickened. The Weigert stain showed complete absence of medullary sheaths.

Jakob, working in Alzheimer's laboratory in Munich, experimented with twenty-four rabbits and three monkeys. The trauma to the head was produced with the animal in a state of ether narcosis by subjecting the left parietal region to direct trauma by means of a hammer falling by its own weight one or more times. In the experiments on the cord the Schmaus technic was followed. In rabbits with injury to the brain the duration of life and the changes after concussion were as follows:

No. of Animal	No. of Traumas Inflicted	Duration of Life	Results
1	1	24 hr.	Normal brain
2	2	2 min.	No bleeding in brain substance
3	1	2 min.	Normal brain
4	1	Immediate	No bleeding in brain substance
5	3	7 days	High grade destruction of ganglion cells and nerve fibers; no petechiae
6	3	7 days	Same as rabbit 5
7	10 (Oct. 20) 4 (Oct. 23)	13 days	No changes in ganglion cells; degeneration in pyramidal tracts and Monakow's bundle; no petechiae
8	2 (Jan. 19) 1 (Jan. 21)	18 days	Degeneration of nerve cells and axis-cylinders; petechiae in gray matter of brain and upper part of cord
9	6 (Nov. 22)	21 days	Petechiae in caudate nucleus
10	2	38 days	Petechiae in region of central canal of cord
11	3	31 days	No petechiae; severe degeneration in pyramidal and rubrospinal tracts

No. of Animal	No. of Traumas Inflicted	Duration of Life	Results
12	2 (Sept. 21) 1 (Sept. 22)	59 days	Petechiae in central gray matter of medulla; degeneration in cells of pons and medulla; degeneration of fibers; appearance of chronicity
13	3 2 (Dec. 18)	5 mo.	No petechiae; gitter cells and degenerative process appearing at age of about 50 days; many empty spaces
14	2 (Sept. 19) 10 (Oct. 20) 4 (Oct. 26)	81 days	Most striking feature was great number of petechiae and areas of softening in different stages of pathologic change

In rabbits with trauma to the cord the results were:

RABBIT C.—The rabbit died in three quarters of an hour. There were numerous hemorrhages in the gray matter.

RABBIT D.—The animal lived twenty-one days. Hemorrhage occurred at the border of the gray and the white matter.

RABBIT H.—The animal lived four months. In the anterior horn of the dorsal portion of the cord were fresh perivascular hemorrhages without evidence of damage to the vessels.

RABBIT K.—The animal lived seven days. There was hemorrhage in the gray matter of the dorsal part of the cord.

In a section devoted to capillary apoplexy, Jakob concluded that trauma acts by tearing and crushing the essential nerve elements and that the capillary hemorrhages are secondary phenomena. He was at a loss to explain the relatively fresh hemorrhages in the older traumatized animals (animal 14, eighty-one days). "Das Auffallendste an diesem Tiere bleibt die grosse Zahl der Blutungen und Erweichungen von gänzlich verschiedenem Alter."[3] The site of predilection of these punctiform hemorrhages was the medulla oblongata and the upper cervical region, although they were seen also in the white substance. The inconstancy of their occurrence could be considered only as incidental. Four animals used as controls which were killed by hanging showed no punctiform hemorrhages. In the majority of animals a slight but definite glial proliferation could be demonstrated in the surrounding tissue. However, in a rabbit which survived four months there was no reaction in the surrounding tissue accompanying fresh hemorrhages. In this connection the conception of traumatic late apoplexy was discussed. Bollinger expressed the belief that trauma causes a mechanical irritation of the nerve tissue, which gradually produces an (indirect) irritation of

3. The most striking change in this animal is the large number of hemorrhages and areas of softening of various ages.

the wall of the vessel and finally rupture. Langerhans and Israel contested this thesis. Jakob, however, expressed not the slightest doubt that in his monkeys the larger macroscopic hemorrhages were the result of traumatized tissue. (Sick monkeys! Colitis.) (In two of three animals there had previously been operation on the brain!)

Jakob admitted that there was no explanation for the occurrence in the older traumatized animals of fresh hemorrhages in unaltered nerve parenchyma without demonstrable defect of the vessels. Von Friedman made the same observation in human material obtained after trauma. One must, however, admit the existence of late apoplexy. He cited Fischer in drawing an analogy between concussion and Goltz' tapping experiments. Traumatic paralysis of the cerebral vessels may be produced, especially of the rich vascular network of the cerebral hemispheres. The concussion may take place either in the cerebral vessels predominantly or in connection with vessels of the general vascular system, which may be followed by serious results. He also cited the celebrated experiments of Koch and Filehne, who avoided the complications of gross mechanical injury by employment of repeated taps or traumas. These investigators attempted by this means to show that not merely one but all brain centers were injured. This was proved by isolating the different centers by appropriate experimental methods, which showed immediate and similar effects.

Ricker [4] expressed the belief that pathologico-anatomic lesions of the brain following concussion are dependent on the state of the vasomotor system. He referred to the work of Schiff (1856), who demonstrated the presence of vasodilator fibers in the ear vessels of the rabbit after slight mechanical stimulation. This was accompanied by an increase in the blood flow. Strong mechanical stimulation of the ear vessels produced a white, anemic area, followed by uniform reddening and petechiae. This phenomenon was interpreted as initial vasoconstriction and subsequent dilatation of such a degree that diapedesis occurred. Observation of the mesentery of the rabbit demonstrated that diapedesis occurred only when marked slowing of the blood stream approached stasis—i. e., prestatic circulation.

With mechanical stimulation four types of response were demonstrated: (1) widening of the blood stream and increase in flow—fluxion; (2) narrowing of the blood stream—ischemia; (3) widening of the blood stream, or slowing of the first grade—inflammation, and (4) widening of the blood stream, or slowing of the second grade—prestatic circulation and stasis. Mechanical, thermal and chemical stimulation had the same effect on the vessels.

4. Ricker, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschütterung in Abhängigkeit vom Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180, 1919.

The loss or diminution of the excitability of the constrictor fibers during the hyperactivity of the dilator fibers was characteristic of the inflammatory and prestatic states (determined by direct observation with the microscope and by micrometry of the width of the vessels and the flow of blood with the animal under the action of epinephrine). In the state of fluxion the constrictor fibers responded to epinephrine.

The application of mesothorium to the rabbit's ear gave evidence of a late and persisting prestatic effect. It was concluded that the late effects of stimulation of vasomotor nerves may be greater than the action of the initial stimulus. It was also concluded that diapedesis can occur in vessels only when the blood is circulating: White softening may be accompanied by preexisting hyperemia and diapedesis; the necrosis appears white with the unaided eye. Red softening occurs only when there is an unusual amount of blood in the tissues, which is unabsorbed and produces pigment. The persisting hyperemia in the prestatic state causes hyperemia of the connective tissue. The slower the circulation the greater the damage to the parenchyma. The general statement and the hypothetic character of this conception were admitted.

Late apoplexy (Bollinger, 1891), which has been interpreted as bleeding by rhexis due to changes in the walls of the blood vessels, was stated by Ricker to be the result of late diapedesis in originally intact brain tissue (and vessels). He qualified this opinion, however, by admitting that in necrosed tissue the wall of the vessel may ultimately rupture; however, this had not been his experience and had not been proved.

The theory advanced by Schmaus, Jakob and others, that at the moment of concussion a serious, irreparable primary damage occurs to the brain tissue, leading to immediate necrosis, could not be accepted by Ricker, for if this were a fact the process would begin in the briefest interval and be consummated in a few days. On the contrary, pathologic examination of tissue showed that the process goes on for weeks and months in various stages of development; even the first stages of the process were demonstrated after this interval. Ricker made the assertion that excessive irritation of nerve tissue will cause only lack of excitability, not destruction. The term contusion (bruising) should be reserved for lesions produced at the instant of trauma and should not be confused with concussion, a vital process; necrosis begins with contusion and ends (if followed by stasis) with concussion.

Numerous American writers have made contributions to the subject of traumatic petechiae. Allen [5] studied the results of impact through

5. Allen, A. R.: Remarks on the Histopathological Changes in the Spinal Cord Due to Impact: An Experimental Study, J. Nerv. & Ment. Dis. **41**:141. 1914.

the intact dura on the spinal cord of the dog after laminectomy. Fifteen minutes after impact exceedingly minute hemorrhagic foci were observed, particularly in the gray matter but also in the posterior columns. These foci were conspicuous two hours after impact, and in places the hemorrhage had become hyaline, showing washed-out ghosts of corpuscles at the edges. After four hours swollen axis-cylinders were demonstrated. The unexplained glasslike appearance of some of the areas was thought to be due possibly to the hemolytic effect of injured myelin on the red cells. However, sterile emulsions of spinal cords failed to produce hemolysis in whole or defibrinated blood.

Cassasa [6] encountered five instances of multiple traumatic cerebral hemorrhages without associated fracture of the skull among many thousand cases in which autopsy was performed. Sudden overfilling of the perivascular spaces with cerebrospinal fluid was conceived to produce laceration of the vessel by tearing its wall in the neighborhood of a fibrillary attachment to the surrounding brain tissue. Passage of cerebrospinal fluid from the surface of the brain, due to pressure exerted in the change in shape of the skull, would otherwise compress but not lacerate the vessel. Osnato and Giliberti [7] reported a case of fatal injury to the brain in which the period of survival was thirty-six hours. There was no fracture of the skull. Petechial hemorrhages were scattered through the centrum ovale, the corpus callosum and the pons. Some of the red cells in the hemorrhagic areas were basophilic. The brain tissue was vacuolated. It was suggested that fibrin thrombi, with basophilic staining reaction, result from concussion due to a disturbance in the colloidal calcium equilibrium, facilitating its precipitation. Many fat emboli were encountered, despite the absence of a fracture of the skull. It was assumed that trauma to the medullary substance of the bones was sufficient to have produced this response. No description or illustration of petechiae resulting from rupture of the vessels was found in this article. Martland and Beling [8] accepted Cassasa's theory and reported twenty-three instances of multiple deep hemorrhages in three hundred and nine cases in man in which the outcome was fatal. A description of the pathologic changes was given in nine instances. The presence of petechiae was determined by failure to wipe the punctate areas of hemorrhage from a freshly cut surface. Petechiae due to rhexis were not demonstrated microscopically.

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6. Cassasa, C. B.: Multiple Traumatic Cerebral Hemorrhages, Proc. New York Path. Soc. **24**:101, 1924.

7. Osnato, M., and Giliberti, V.: Postconcussion Neurosis—Traumatic Encephalitis: A Conception of Postconcussion Phenomena, Arch. Neurol. & Psychiat. **18**:181 (Aug.) 1927.

8. Martland, H. S., and Beling, C. C.: Traumatic Cerebral Hemorrhages, Arch. Neurol. & Psychiat. **22**:1001 (Nov.) 1929.

Winkelman and Eckel [9] reported seven cases of severe injury of the head in which there was microscopic study of the brain. The duration of life in these cases was fifty minutes; three, three, three, four and twelve days, and two weeks, respectively. In five cases petechial hemorrhages were demonstrated. In addition to the petechiae, hyalinization of the walls of the vessels, large spaces outside the walls, areas of softening and coagulation, necrosis, acellular foci, edema and gliosis were described. There was no microscopic demonstration of petechial hemorrhage by rhexis. Winkelman and Eckel did not commit themselves definitely as to the nature of the traumatic petechiae. The incidence of petechiae was strikingly greater in this study than in those reported by other writers.

Rand and Courville [10] studied the state of the brain fibers and the glial reaction in relationship to petechiae. End-bulbs, corkscrew twisting and fragmentation of nerve fibers surrounded these hemorrhages. In the smaller hemorrhages there was no noticeable change in the glia, but in the larger hemorrhages regressive changes were produced by compression, local ischemia and softening, leaving a small, cystlike space surrounded by more or less actively proliferating glia. Glial rings were thus produced. Fat emboli in most cases of injury to the head were due to fracture of long bones.

ANATOMIC INVESTIGATION

The present emphasis on traumatic deep petechial hemorrhages as a cause of traumatic encephalopathy, the various histologic types, the occasional late occurrence, the lack of precise knowledge of their mechanism, the striking similarity to nontraumatic forms and the tendency of some investigators to regard contusion and concussion of the brain as lacking in essential differences led to the present investigation.

Our observation that petechiae were frequent in injured brains prompted an inquiry as to the nature, location and mechanism of these minute hemorrhages—whether they occurred in arterioles, veins or capillaries, by rhexis or by diapedesis, and the time relationship to the injury. Two lines of investigation were pursued: one, examination of a series of injured human brains, and the other, experiments on the albino rat.

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9. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During the Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934.

10. Rand, C. W., and Courville, C. B.: Histologic Studies of the Brain in Cases of Fatal Injury to the Head: IV. Reaction of the Classic Neuroglia, Arch. Neurol. & Psychiat. **27**:1342 (June) 1932; Histologic Studies of the Brain in Cases of Fatal Injury to the Head; V. Changes in the Nerve Fibers, ibid. **31**:527 (March) 1934.

Material.—The human material consisted of a study of eleven consecutive cases of fatal injury to the brain, obtained from the coroner's office of San Francisco. Case 3 was discarded because of a complicating fracture of the neck and case 4 because of complicating meningitis; the material in case 9 was incompletely worked up histologically. In two cases death was immediate; in three, within twenty-four hours, and in one case each, after three and a half, four and eight days, respectively. All the cases were characterized by fracture of the skull, unconsciousness and pial hemorrhages. Gross contusion and surface hemorrhage were not considered in this investigation. All the brains showed some degree of internal stippling. It was obviously impossible to determine by gross inspection whether certain stippled areas were the seat of dilated vessels, thromboses or hemorrhages. The criterion of wiping a fresh cut surface to determine the presence or absence of petechiae, as has been suggested, was not considered trustworthy. Tissues were fixed in formaldehyde and prepared by inclusion in paraffin and pyroxylin. Microscopic sections, as well as frozen sections, from various areas of the cerebral cortex, the central white matter, the basal ganglia, the brain stem and the gray and white matter of the cerebellum were stained with hematoxylin and eosin, hematoxylin and the Van Gieson method, toluidine blue and scarlet red.

Experiments on albino rats are being carried out in the propulsion impact, causing injury of the brain, with various states of concussion and paralytic sequelae. The animals are killed at various intervals, in order to study further late petechial bleeding and the surrounding tissue reactions. In one animal which had a brief period of paralysis of one hindlimb and was killed four days after injury, no pathologic change was observed, save for a small pial hemorrhage in the occipital region. This experiment suggested that concussion resulting in temporary paralysis of the limb was a reversible functional effect, which is in line with our clinical experience.

REPORT OF CASES

Case 1.—S. K., a man aged 68, was severely traumatized when he was struck by an automobile. There were a stellate fracture of the vertex of the skull, fracture of the right clavicle, and of the ribs, puncture of the lung and numerous contusions and abrasions. On his admission to the San Francisco Hospital, he was conscious, talkative, noisy and delirious. There was bleeding from both nostrils. The right pupil was dilated and the left contracted. There was no paralysis or definite abnormality of the reflexes.

The patient died four days after the accident, of cardiorespiratory failure. The coroner's necropsy, performed fourteen hours after death, revealed marked congestion of the pia-arachnoid over the right hemisphere and less over the left. Over the first and second frontal convolutions of the left hemisphere was a hemorrhage, the size of a 50 cent piece, involving the pia-arachnoid and the adjacent cortex, to a depth of 1 cm. No gross hemorrhage was observed below the tentorium. Macroscopic sections showed marked stippling in the left hemisphere and less marked in the right, which contrasted with the greater surface congestion of this hemisphere. Below the tentorium stippled areas, not marked, were observed only in the region of the dentate nuclei. The arteries of the brain were in good condition for the age of the patient.

Microscopic Pathologic Changes.—A study of the stippled areas in the right hemisphere and the subtentorial region was made from frozen sections and from pyroxylin and paraffin inclusions. The sections were stained with hematoxylin

and eosin, hematoxylin and the Van Gieson method, the Nissl method and scarlet red. Sections of the superior part of the precentral convolution were characterized by hyperemia and distention of the vessels. There was no free blood in the cortex or evidence of vascular rupture or blood in the perivascular spaces of any of the vessels examined in the gray matter of the cortex proper. Petechiae were present in the central white substance, among many dilated vessels. In one vessel red cells were seen passing through the interstices of the wall, which showed degenerative changes in the endothelium and the elastic layer. In the thalamus occasional accumulations of irregular nucleated cells were observed, as though by disintegration of thin-walled, thrombosed vessels. In the lenticular nucleus there were areas of diffuse accumulation of blood in the tissues, apparently not from any one vessel. In a large, engorged vein the walls were undergoing disorganization, and beginning thrombosis was apparent, evidenced by marked accumulation of leukocytes. Blood surrounded the vein for a considerable distance. In the caudate nucleus the same dilatation of veins and capillaries with stasis

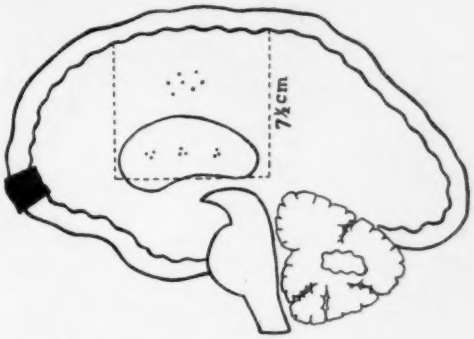

Fig. 1 (case 1).—Diagrammatic representation of the brain, in which were pial hemorrhage, contusion and laceration of the left frontal lobe; vascular congestion over the hemispheres, more marked on the right; marked stippling throughout the left hemisphere and less in the right; stippling about the dentate nucleus; petechiae in the cerebral white and gray matter, and frequent thromboses. There was no evidence of tears in the vessels.

was apparent. Hyaline changes and the accumulation of white cells were frequently seen in vessels which showed no signs of rupture.

The midbrain, the pons, the medulla and the cerebellum showed a characteristic picture of thrombosed vessels, with a striking absence of hemorrhages in the tissues or surrounding the thrombotic vessels. An area in the lower portion of the pons showed infarction resulting from a thrombotic process in a small vessel, the necrosis extending to the surrounding tissue. The vessel was outlined only by cellular elements, the wall having become disintegrated, and within the area of this blood vessel many large cells were filled with pigment, showing large nuclei and some vacuoles. Similar cells in the periphery of the infarct contained no pigment and showed multiple nuclei. They were evidently scavenger cells of a transitional type and not polymorphonuclear blood elements. No instance of traumatic rupture was observed. Simple dilatation of vessels was frequent.

It was apparent that the stippled appearance of the gross section of the right hemisphere was due not solely to petechial hemorrhage but, in the majority of

vessels, to dilatation and stasis. Thus, the distribution of blood in the two hemispheres was explained by cortical congestion in the right hemisphere and subcortical congestion in the left. A block from the left hemisphere (fig. 1), measuring 2.5 cm. in thickness, which extended from the white matter to the cortex and anteriorly from the region of the posterior ventricular horn, was included in pyroxylin. Serial saggital sections were cut at 50 microns, and 430 cuts were made. Every fifth cut was stained, the distance between the sections being, therefore, 0.25 mm. Hemorrhagic areas in the serial sections were given subnumerations and were followed until the areas disappeared. For example, in serial section 4, area 1, a diffuse patch of hemorrhage into the wall of the ven-

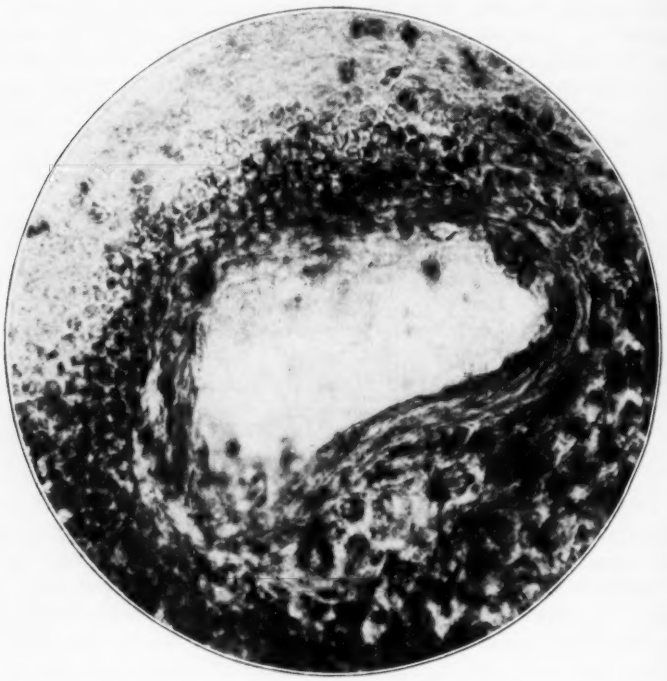

Fig. 2 (case 1).—Photomicrograph (× 450) of a petechiae formed by diapedesis.

tricle, was followed through ten sections, representing 2.5 mm., without any evidence of rupture of the vessel. Four such areas, including regions of perivascular hemorrhage, were likewise followed, without evidence of tearing of any vessel. A thrombosed vein was followed 3 mm., without evidence of tearing. In one part of the vessel perivascular accumulations of blood cells were observed; in another the vessel was empty of blood. There were perivascular petechiae in which the blood outside the wall appeared recent. In no area thus followed in serial sections was a frank rupture of the vessel observed. The characteristic appearance of the altered vascular wall was degeneration and disorganization. Fat emboli were not observed.

CASE 2.—F. E. M., a youth aged 19, was brought to the emergency hospital in an unconscious condition, with fracture of the skull, after an automobile collision. He bled from the left ear. There were a Babinski sign bilaterally, equal and dilated pupils and the Cheyne-Stokes type of respiration. Death occurred one hour after injury. The coroner's necropsy, performed seven and a half hours after death, revealed that the pial vessels over the vertex of the cerebrum were congested and those of the base less so. The pia over the cerebellum was markedly congested. Small pial hemorrhages were present in the lateral fissure and over the superior frontal gyrus and the cuneus on the left and over the right vertex. There were no lacerations of the brain surfaces or evidence of tearing of the vessels. In gross sections many scarlet punctate areas were observed in the central gray and subcortical white matter of both cerebral hemispheres, in the caudate nucleus and in the tegmentum. The cerebellar white matter and the medulla appeared pale, without definite vascular markings. A hemorrhagic area was visible in the pons, owing to rupture of a vessel.

Microscopic Pathologic Changes.—The cerebral cortex was characterized by edema, distention of the vessels and a vacuolated appearance, especially in the frontal region. No petechial hemorrhages were observed in the cortex. The central white matter also showed a vacuolated, sievelike appearance. Perivascular petechiae were present in the subcortex of the temporal region. In paraffin sections a considerable reaction about the smaller blood vessels and the ganglion cells was interpreted as due to fixation. In the thalamus small hemorrhages, not limited to the perivascular space, were present without evidence of tearing of the vessels. The thalamus, as well as the lenticular nucleus, presented the appearance of edema. The tegmentum showed marked distention of the vessels. In the ventral portion of the pons there was a relatively large hemorrhage due to rupture of a vessel. Stranding, cleavage and edema of tissues were observed in the cerebellum, but no hemorrhages or petechiae.

CASE 5.—E. A., a man aged 39, was found unconscious in his garage and died thirteen hours later, of an injury of undetermined character. The coroner's necropsy, performed fifteen hours after death, revealed a fracture in the right parietal region of the skull, but no gross contusions or lacerations of the brain. There were a wide band of pial hemorrhage from the vertex to the temporal lobe of the right hemisphere and large patches of hemorrhage over the precentral and the postcentral cortex and the frontal tip on the same side. The left hemisphere showed vascular congestion and a small pial hemorrhage over the cuneus. Cut sections showed stippling in the central white and the gray matter. Petechiae were present in the subcortical white matter, the thalamus and the midbrain and sparingly in the thalamus. The corpus callosum showed areas of yellowish discoloration. There was a small area of softening in the right postcentral convolution. No tears were demonstrated in the vessels.

Microscopic Pathologic Changes.—In the second and third cortical layers of the right precentral and temporal regions sievelike areas were seen, similar to those observed in the white substance. Perivascular petechiae, thromboses and vacuolation were frequent in the subcortex. The precentral cortex beneath the pial hemorrhage showed no gross defects but great distention of all vessels, especially the capillaries. Perivascular petechiae were present in the cortex proper, in two of which was rupture of the vessel. In the corpus callosum there were small areas of diffuse hemorrhage, without definite demonstration of perivascular bleeding. The cells of these hemorrhages had undergone lysis. The thalamus

showed well marked petechiae, with large perivascular, closely packed hemorrhages. In none of these petechiae were tears in the vessels demonstrated. The caudate and the lenticular nucleus showed marked widening of the perivascular and the perineural spaces but no petechiae. Large perivascular petechiae were present in the midbrain; in addition to many dilated vessels, there were shredding and a sievelike appearance of the tissues. In the pons and the medulla the most marked condition was a sievelike appearance of the tissues, but no petechiae were noted. The appearance of the cerebellum was normal.

Case 6.—E. S., a structural iron worker, was struck by a falling girder, which fractured his skull. He was dead on his arrival at the receiving hospital. Necropsy, performed nine hours after death, revealed extensive pial hemorrhages over the frontal and the parietal lobe on the left and the dorsal part of the cerebellar lobes and the vermis. Patchy pial hemorrhages were seen in the right hemisphere, and a large hemorrhage was present in the interpeduncular space. There was stippling of the basal nuclei and, to a lesser degree, of the central white substance of the hemispheres.

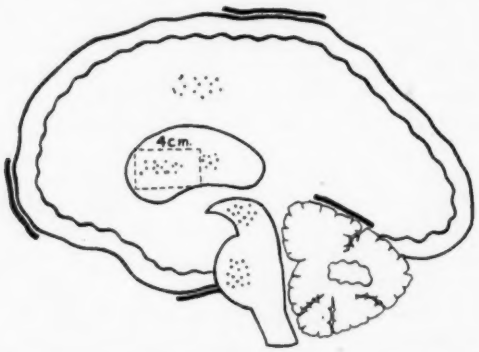

Fig. 3 (case 6).—Diagrammatic representation of the brain, in which were extensive surface bleeding; absence of lacerations, and presence of petechiae, without evidence of tearing of the vessels.

Microscopic Pathologic Changes.—Petechiae were observed in the thalamus and the corpus striatum on both sides, the midbrain, the pons and, to a less marked degree, the central white matter of the hemispheres. No petechiae were present in the cerebral cortex or in any part of the cerebellum. The character of the petechiae is shown in photomicrographs of a portion of the left corpus striatum (figs. 4 and 5). In that region there was a remarkable picture of hemolysis, both within and without the wall of the vessels, with basophilic staining reaction of the contents. The petechiae occurred about the arterioles, in the walls of which no definite pathologic alteration could be demonstrated. The intact capillary network of the cerebral cortex was well brought out by the toluidine blue stain. No definite tear was seen in any vessel showing a petechial hemorrhage. A block, measuring 4 by 2 by 1.2 cm., from the right corpus striatum was serially sectioned at 60 microns. Three vessels in the putamen showing perivascular hemorrhages were followed through this block, without any evidence of tearing or hemorrhage by rhexis.

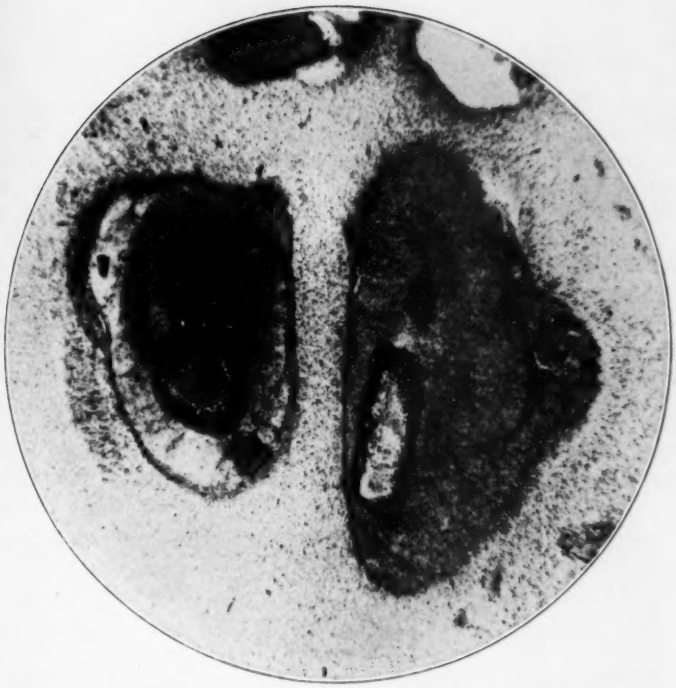

Fig. 4 (case 6).—Photomicrograph showing petechiae in the corpus striatum.

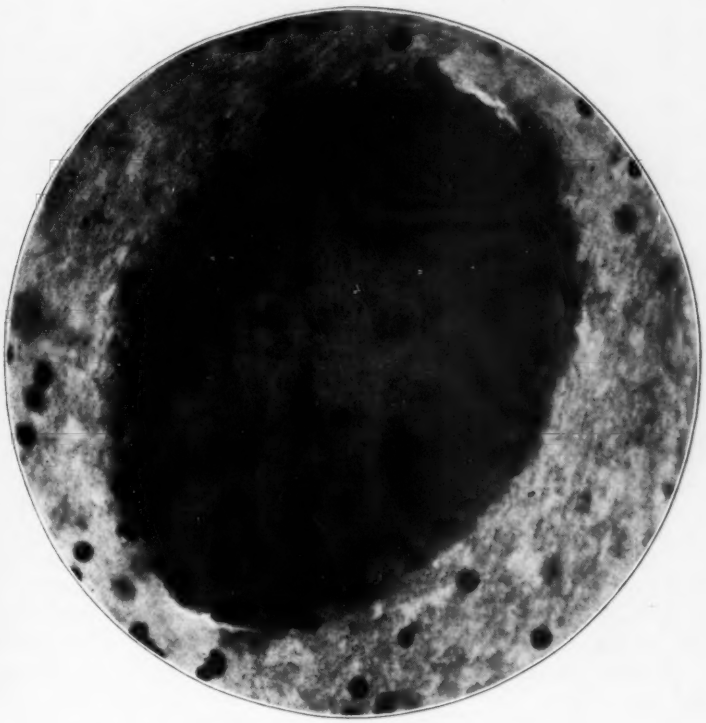

Fig. 5 (case 6).—Photomicrograph showing hemolysis.

Case 7.—J. K., a woman aged 44, was injured in an automobile collision and rendered unconscious. There were lacerations of the scalp in the left frontal area, fractures of the ribs and skull, bleeding from the right ear and both nostrils, weakness of the left extremities, and a Babinski sign bilaterally. During the following days the patient remained semiconscious and was difficult to arouse; speech was incoherent; there were twitching of the left side of the face and difficulty in swallowing. Death occurred eight days after the accident. The coroner's necropsy, performed seventeen hours after death, revealed vascular congestion over the occipital lobes and the right parietal lobe. The right occipital lobe presented a few small pial hemorrhages. There was no evidence of contusion or laceration of the brain surfaces. The hemispheres, cut in sagittal sections, showed stippling in both the white and the gray matter. The upper part of the posterior three fourths of the corpus callosum presented a marked multiple hemorrhagic condition. In the white substance of the right cerebellar hemisphere there was a large thrombosed vessel, with branches extending toward the cortex.

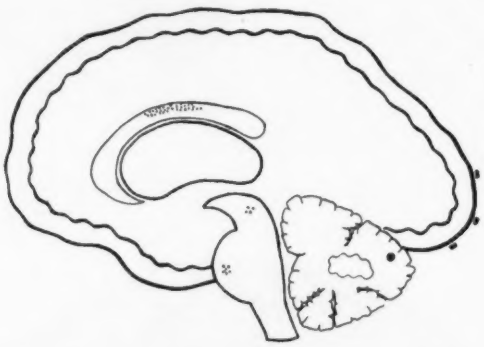

Fig. 6 (case 7).—Diagrammatic representation of the brain in which were slight pial bleeding; stippling in the central white and gray matter; marked presence of petechiae in the corpus callosum, which were otherwise infrequent, and no evidence of tearing of the vessels.

Microscopic Pathologic Changes.—No petechiae were observed in the cerebral cortex, although there were numerous dilated vessels. About some arterioles vacuolated areas were present, such as were frequently observed in the white matter. In the second and third frontal cortical layers a similar honeycombed, vacuolated appearance was noted.

The hemorrhagic area of the corpus callosum presented many diffuse streaks of hemorrhage and ring and ball hemorrhages, with no evidence of tearing of the vessels. Diffuse staining showed damage to the endothelium and degeneration of the walls of the vessels. The contents of the lumen often appeared hyaline. Preserved red cells were present in the extravasated blood; other cells were in the process of disintegration. Little, if any, phagocytosis was present, and there were no deposits of pigment. The white matter of the corpus callosum showed a marked honeycombed appearance. Except in the corpus callosum, petechiae were rarely observed in the brain, and only in the midbrain and the pons. In these localities the hemorrhages were of the perivascular form, with well preserved red cells. Widening of the perivascular and the perineural spaces was marked. A sievelike appearance of the white matter was frequent about the vessels. There

were no fat emboli in any part of the brain, but accumulation of fat globules was occasionally seen in the tissues and about the walls of the vessels. The central white matter of the cerebellum showed a large thrombosed vessel with fibrin formation; a thrombosed vessel of the cerebellar cortex contained a marked fatty deposit in the wall. The arteries of this brain showed moderate sclerosis.

This patient, therefore, presented remarkable variations in the state of the smaller vessels of the brain—dilatation, fresh petechiae and thromboses, with hyaline and fibrin changes in the contents, hyalinization and disintegration of the walls and ball and ring hemorrhages.

CASE 8.—L. Y., an adult Chinese man suffering from pulmonary tuberculosis, was killed instantly by a suicidal leap from a hospital window. Necropsy performed six and one-half hours after death, revealed that the skull was fractured. Large bilateral pial hemorrhages were present over the vertex, the right temporal lobe, the right frontal tip and the left parieto-occipital junction. A few small pial hemor-

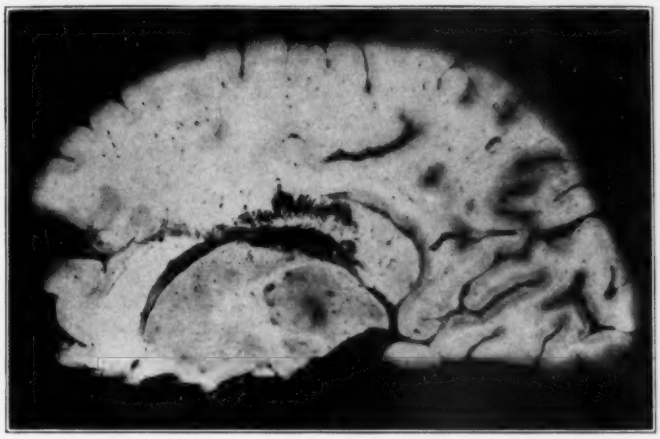

Fig. 7 (case 7).—Photograph of a gross section of the brain, showing multiple petechiae in the corpus callosum.

rhages were observed on the inferior and lateral surfaces of the right cerebellar hemisphere. Sections of the brain showed stippling in the central white matter of both hemispheres, the basal ganglia, the pons and the white matter of the cerebellum. Blood clots were present in the left lateral ventricle and the fourth ventricle. The left vena terminalis was filled with a firm clot; there were also clots in the veins of the left taenia semicircularis. There were no lacerations.

Microscopic Pathologic Changes.—Well marked perivascular petechiae were observed in the white matter underlying the frontal tip and the temporal cortex of the right hemisphere and in the thalamus. No area of the cortex showed petechiae. Examination of the central white matter, the pons and the cerebellum, which showed stippling on cut section, revealed no definite petechiae. The appearance in the cerebellar white matter was one of vacuolation and vascular dilatation, with enlargement of the perivascular spaces. In contrast to this picture, the cortex and white matter of the cerebellum between the folia presented a compact picture, like that of a book-plate.

Many of the cerebral blood vessels were engorged with blood; others showed apparently laked blood and globular basophilic masses within the lumen, as well as gaseous globules, hyaline contents and fibrin. Large clear areas surrounded the numerous vacuolated regions. Such areas beneath the cortex were sharply demarcated at the junction of the gray and the white matter. The right vena terminalis presented a picture of coagulated plasma filling the lumen, in which

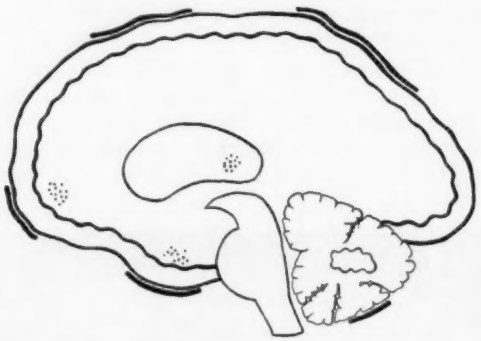

Fig. 8 (case 8).—Diagrammatic representation of the brain, in which were extensive pial hemorrhages and blood in the ventricles; stippling in the cerebral white matter; petechiae in the subcortical white matter and the basal ganglia, and no evidence of tearing of the vessels.

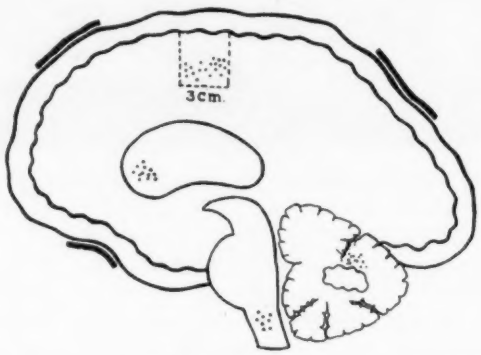

Fig. 9 (case 10).—Diagrammatic representation of the brain, in which were extensive pial bleeding over the cerebral hemispheres; stippling above and below the tentorium; lacunae in the left lenticular nucleus; advanced arteriosclerosis, and presence of petechiae but no tearing of the vessels.

were areas of pigmentation and disorganized blood cells staining with hematoxylin, with no evidence of red cells, even shadow forms. The picture was difficult to explain, on the basis either of the effects of immediate death or of postmortem changes, and presented the protean nature of changes observed in acute conditions.

Case 10.—M. C. R., a man aged 72, was struck by an automobile, causing fracture of the skull and death within fifty-five minutes. Coroner's necropsy,

performed eighteen hours after death, showed large pial hemorrhages over the precentral, occipito-parietal and temporal cortex on both sides, without underlying laceration of the brain substance. Stippling was present in the central white matter of both hemispheres, the pons, the medulla and the cerebellar white substance. There was a high degree of arteriosclerosis. Lacunar defects were present in the left lenticular nucleus.

Microscopic Pathologic Changes.—Petechiae were observed in the central white matter of the cerebral hemispheres, the lenticular nuclei, the medulla and the cerebellar white substance. In the left lenticular nucleus, surrounding intact

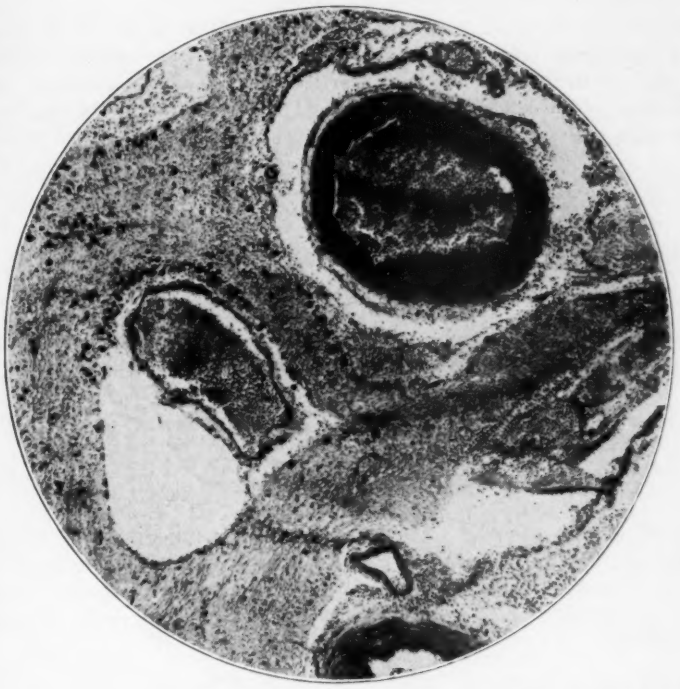

Fig. 10 (case 10).—Photomicrograph showing lacunae in the left lenticular nucleus; perivascular hemorrhage surrounding a large arteriole and numerous gitter cells in the degenerating parenchyma.

blood vessels, were a number of lacunae, about which were recent petechiae. The walls of these vessels showed hyaline changes. Numerous gitter cells were present in the walls of these lacunae and in the disintegrating brain tissue. The medulla and the cerebellar white matter showed occasional diffuse hemorrhages. In the cerebellum the hemorrhages surrounded intact arteriosclerotic vessels. A group of these vessels showed individual perivascular hemorrhages, representing areas approximately ten times the size of the vessels. A block for serial sections from the central white matter of the left hemisphere, measuring 10.5 mm., was fixed in pyroxylin and cut at 35 microns. Two hundred and ninety-five sections were cut, and every fifth section was stained. The serial distance of each section examined

was 0.175 mm. The vessels in the stippled area showed the usual picture of dilatation, hyalinization of the contents and perivascular petechiae, but no tears. The capillary network, well brought out in sections stained with toluidine blue, showed no evidence of hemorrhages; the petechiae were in relationship to the arterioles. The sections showed numerous areas of disintegrated brain tissue, with shredding and edema, not, however, in any definite relationship to the vessels. Sections of the right lenticular nucleus stained with hematoxylin and scarlet red showed a few fat emboli. The pathologic picture of the brain was one of advanced arteriosclerosis and extensive petechiae, without evidence of rupture of the vessel. The lacunae in the left lenticular nucleus were obviously due to an old, progressive process, with the recent addition of petechiae.

Case 11.—J. W. A., a man aged 70, was injured by a fall on the street and entered the hospital unconscious. There were a laceration of the scalp and bleeding from the left ear; the skull was fractured. There were no pathologic reflexes. Examination of the left eye showed a cataract and fixation of the pupil to light. Bloody fluid was removed by spinal tap. Unconsciousness persisted until death,

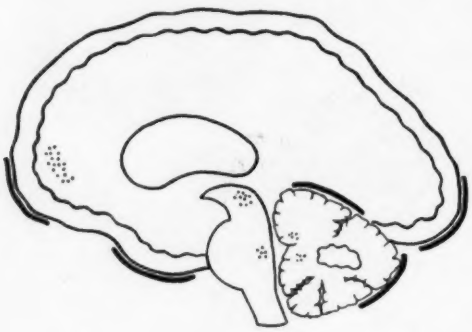

Fig. 11 (case 11).—Diagrammatic representation of the brain, in which were extensive pial hemorrhages; stippling above and below the tentorium; ring hemorrhages in the subcortex of the frontal lobe; perivascular petechiae in the midbrain and the surrounding portion of the fourth ventricle, and no evidence of tearing of the vessels.

three and a half days after the injury. The coroner's necropsy, performed nine hours after death, revealed extensive pial hemorrhages over the right frontal and temporal poles, the left temporal and occipital poles and the upper and posterior cerebellar surfaces. The basal vessels were markedly sclerotic. In gross sections marked stippling was seen in the subcortical white matter beneath the meningeal hemorrhage of the right frontal lobe, at a depth of 1.5 cm. Stippling was also present subcortically beneath the left temporal pole. There was no laceration or global hemorrhage in these localities. With these exceptions the interior of the hemispheres showed no stippling. Stippling was present in the tegmentum at the level of the posterior quadrigeminal bodies, in the pontile portion of the tegmentum and in the cerebellum bordering the fourth ventricle.

Microscopic Pathologic Changes.—There were many unaltered, dilated vessels. The area of stippling in the frontal lobe showed a picture of petechial ring hemorrhages. A slide showed approximately twenty such hemorrhages, consisting of densely packed red cells fairly well preserved and with good contour. Many of

these hemorrhages surrounded a clear, circular area, in the center of which was a vessel with the wall intact, staining poorly with hematoxylin and eosin and the Van Gieson stain. The interior of a number of these vessels contained basophilic thrombotic masses. The surrounding clear area was unstained and contained a few cells with polymorphous basophilic nuclei. Other petechiae assumed the form of ball hemorrhages, in which could be detected no central vessel or the ordinary form of perivascular hemorrhage by diapedesis. The hemorrhage in the midbrain was characterized by the ordinary petechial forms. In this brain there was no demonstration of hemorrhage by rhexis. In the roof of the fourth ventricle were areas of infiltration of blood in the tissues, without definite

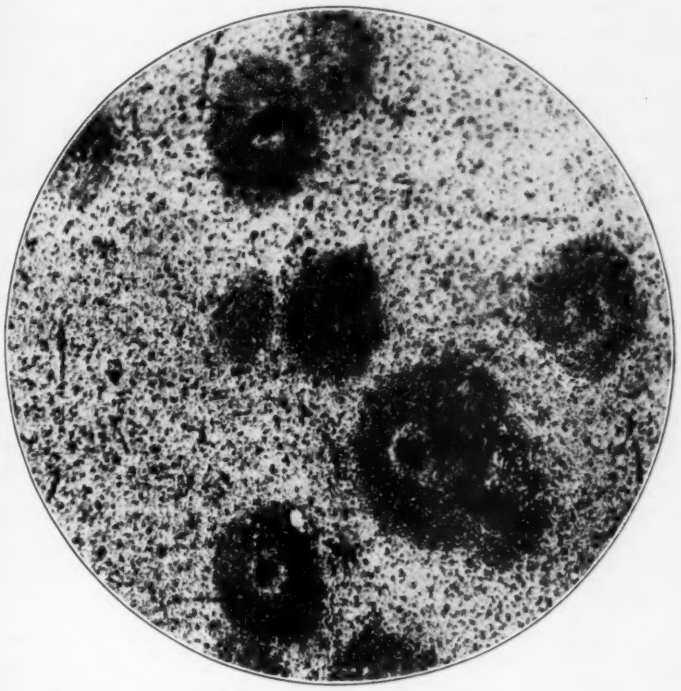

Fig. 12 (case 11).—Photomicrograph showing ring hemorrhages in the subcortex of the frontal lobe.

relationship to the vessels. In other areas perivascular petechiae occurred, and in others, thrombosis with hyalinization of the contents of the vessels, and deposits of fibrin. Vacuolation was seen in the parenchyma. The floor of the fourth ventricle showed the same picture, to a lesser degree. The picture was striking in that the hemorrhages were much larger than could reasonably be accounted for by diapedesis and suggested rupture of vessels, which, however, could not be demonstrated. In the roof of the fourth ventricle amylaceous bodies were seen.

The brain showed vascular changes similar to those in cases 1 and 7, in which death occurred an appreciable interval after trauma: namely, vascular dilatation, hyaline and thrombotic changes and fresh perivascular and ring hemorrhages.

COMMENT

Study of these cases of severe and fatal injury to the head revealed that deep hemorrhagic petechiae were present in all instances to a greater or less extent and that the mechanism of the ordinary forms was not satisfactorily explained by traumatic tearing of the vessels. In cases of immediate death or in those of death after a short interval, no definite anatomic alteration of the walls of the vessels was presented to account for the production of perivascular petechiae by diapedesis, and it must be assumed that the petechiae at this stage were dependent on a disturbance in the vital function of the wall. Ring hemorrhages were observed only in the cases in which the patient survived longest (cases 1, 7 and 11), and in this type the vascular changes were constant. Internal traumatic hemorrhages due to tearing of the vessels undoubtedly occur and may explain the diffuse and cleft hemorrhages and the massive hemorrhagic foci. However, as compared with the other vascular changes which have been described, they were rare and were absent in cases 6 and 8. Petechiae were observed in the cortex only in case 5. This was the only case in the series in which tearing of vessels was demonstrated in relationship to the petechiae. It is suggested that, because of this observation, the mechanism in this case was one of contusion rather than of concussion. Courville observed a case (personal communication) in which petechiae predominated in the cortex—a rare occurrence, as the cortex is spared in the vast majority of cases reported. We suggest that they may occur as the result of an unusual force and direction of the trauma; otherwise, they would be frequent in the cortex by reason of the proximity to trauma and vascularity. In the spinal cord the reverse is the rule (Jakob's experiments on the cord): Petechiae in the central gray matter predominate over those in the superimposed white matter. This fact lends support to the theory that the effect of concussion is greatest where there is lack of adjustment between the gray and the white substance because of the difference in specific weights (Ferrari, Kocher, Tillman and Apfelbach).

We have, therefore, an anatomic point of differentiation of the effect of contusion and that of concussion on the cerebral vascular apparatus. Other points of differentiation are the appreciable variation in the character and extent of the visible lesions and, finally, the reversible action in concussion, as compared with that in contusion. All these considerations, in connection with our clinical experience, lead us to conclude that contusion and concussion are distinctly different. The researches of Schmaus [2] and Jakob [1] appear to have established the degenerative action of severe concussion on the essential nerve tissues. It is a fair assumption that a similar effect may take place on the cerebral vasomotor innervation. Perivascular petechiae were frequent about the

smaller arterioles and rare about the capillaries, suggesting the rôle of disturbance in innervation. In some instances considerable variation in the state of the smaller vessels was encountered: dilatation, diapedesis, hyaline degeneration of the walls and contents, thromboses, with basophilic staining reaction, perivascular petechiae, ring and ball hemorrhages and, in cases in which the period of survival was longest, a combination of these changes. These observations suggested not only a pathologic sequence but a process with different pathologic stages. The stippled areas were not necessarily hemorrhagic. Changes resembling postmortem effects were noted by previous authors (Osnato and Giliberti [7]). Marinesco [11] expressed the belief that concussion acts on proteolytic ferments of the cells. Mott [12] spoke of commotional shock, due to dislocation of the static equilibrium of colloids, and of late surgical shock, due to absorption of histamine or toxic subctances. Whereas postmortem and agonal effects may account for some of the changes in the vessels noted in the cases in our series, a careful appraisal of the material rendered this improbable in the majority of instances because of the excellent preservation and staining reaction of the tissues in general and the stages of the pathologic changes. Fat emboli, emphasized as an important factor in traumatic petechiae, were not prominent in our cases. Dietrich [13] studied ring hemorrhages in a case of concussion of the brain and concluded that endothelial injury with resulting hemorrhage was produced by vasomotor disturbances. He expressed the belief that hyaline thrombi of the central vessels are a traumatic effect; he observed fibrin stars, generally considered to be of postmortem origin, only at the site of the injured endothelium.

Baker [14] discussed petechial hemorrhages and reported twenty cases of this condition in association with various diseases, including one of "traumatic encephalitis." In a section on microscopic alterations in the normal brain he stated that small extravasations consisting of a few cells partially surrounding the vessels may occasionally be observed. He claimed that a severe perivascular hemorrhage is a definite lesion. Ring hemorrhages, with clear, uninvolved centers, were stated to be due to rupture of tiny capillaries surrounding the larger vessel. Ring hemorrhages were interpreted by us as due to a late stage of the peri-

11. Marinesco, G., cited by Ingvar, S.: Centrifugation of the Nervous System —A Method for Neurocytologic Study: An Experimental Investigation of Cellular Changes in Commotion, Arch. Neurol. & Psychiat. **10**:267 (Sept.) 1923.

12. Mott, F.: The Neurological Aspects of Shock, Lancet **1**:519 (March 12) 1921.

13. Dietrich, A.: Entstehung der Ringblutungen des Gehirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **68**:351, 1921.

14. Baker, A. B.: Hemorrhagic Encephalitis, Am. J. Path. **12**:185 (March) 1935.

vascular petechial process, active diapedesis having ceased in a completely static circulation. Thus, the extravasated blood is forced to the periphery of the perivascular space and into the tissues by an accumulation of tissue fluid in the perivascular space. Ball hemorrhages, in which no central vessel is demonstrated, may be produced by a section cut off center from the central vessel.

The theory of Cassasa [6] that hemorrhagic petechiae are due to rhexis is speculative; it has not been proved histologically and cannot be supported by the law of hydrostatics. As Cobb [15] pointed out, the mouth of the perivascular space at the entrance to the subarachnoid space is small and is supported by a ring of connective tissue, even though the space behind it may be dilated. The circulation in the perivascular spaces is likened to the flow of water in a swamp, not a brook. If Cassasa's theory were valid, petechiae would be more frequent in the cortex, which is not the case.

Our experiments on animals confirmed the observations of other investigators in that the effects of concussion were produced by appreciably less trauma when repeated, thus lending support to the theory of "punch drunk," as advocated by Martland.[16]

Exceedingly small traumatic defects in the walls of the vessels may not have been demonstrated by the microscopic study of serial sections undertaken in this investigation, as it is conceivable that unless serial sections are made corresponding to the diameter of a red cell such defects may escape observation. However, in the ordinary type of rupture of a blood vessel elsewhere in the body, one usually finds a longitudinal tear of some length, and this is probably true of vessels in the brain. Tears which we have observed correspond to this type: A cross-section of the vessel appears with turned-back edges, like the mouth of a vase or the Greek Ω.

In order to standardize the trauma and to conform as much as possible to the mechanism of propulsion impact in the experiments on animals, we devised a lever falling by its own weight, at the long end of which there is a zipper pocket. In this the animal is fixed, the head alone being exposed. By varying the height of the lever, any degree of concussion may be produced. The position of the animal's head determines the site and the direction of the traumatic force affecting the brain. Such controlled experiments may elucidate further the problems under discussion.

What is the symptomatic and clinical significance of traumatic petechiae affecting brain function? Petechiae limited to the perivascular

15. Cobb, S.: The Cerebrospinal Blood Vessels, in Penfield, W. M.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 599.

16. Martland, H. S.: Punch Drunk, J. A. M. A. **91**:1103 (Oct. 13) 1928.

spaces are probably completely absorbed, but those invading the parenchyma cause demyelinization and degeneration of ganglion cells followed by reparative gliosis or cavitation, as in ordinary hemorrhage. The final result of this process is impairment of brain function, clinically designated as traumatic encephalopathy. This terminology appears to us far more precise than "traumatic constitution," a vague term, or "traumatic encephalitis," which implies an inflammatory reaction, or "concussion neurosis," which suggests disturbance of function rather than structural change. In cases of severe injury to the head followed by protracted unconsciousness, but without focal signs, there is a group in which the condition is not frankly of psychoneurotic origin and has been described symptomatically as the posttraumatic head syndrome. This symptomatology may be properly ascribed to disseminated organic lesions resulting from the effects of concussion, including petechial bleeding

An obscure chapter in traumatic encephalopathy is the occasional occurrence of late traumatic effects, referred to in the literature as late apoplexy and late softening. In such cases the condition can be reasonably explained only on the basis of a progressive pathologic process affecting the cerebral vascular system. The normal function of the vascular system is dependent on a properly functioning vasomotor apparatus. According to our thesis, concussion interferes with normal vasomotor function. If persistent, a vicious circle may be established. Prestasis, edema and anoxemia cause degeneration of tissues. The damaged blood vessels are further affected by the tissue alterations which they produce, and, by reason of such progressive and reciprocal changes, late hemorrhage from rupture of the vessels or late softening by thrombosis may occur.

Finally, it cannot be too strongly emphasized that this study of petechial hemorrhage is not proposed to explain the whole pathologic picture of traumatic encephalopathy and that the vascular damage may be less important than direct injury to the essential nerve tissues, as assumed by earlier writers. The first changes predisposing to petechiae, that is, vasodilatation and prestasis, may be considered as a reversible process and may explain the recovery from concussion in the far greater proportion of cases. It is not amiss to quote Osnato and Giliberti [7] on this point:

> Surely in the vast majority of cases of concussion, recovery with almost complete resolution of the diffuse hemorrhagic process takes place, even granting that this occurs to a varying degree in every case of concussion of the brain. It has not been realized, perhaps, how many people in the general population have suffered concussion without, however, so far as one is able to judge clinically, showing any lasting effects. Taking into consideration the number of children who have had falls with resultant injury to the head and varying degrees of the

concussion syndrome, and the great number of boys who have concussion in consequence of injuries while at play, and including also those who in adult life fall from horses, suffer automobile accidents and industrial injuries of various kinds, one can form a picture of the enormous number of persons in the general population who have, at some time or other, suffered a concussion of the brain. Nevertheless, permanent disabling clinical phenomena following concussion of the brain, with or without fracture of the skull, are not commonly encountered. This is in line with our experience with craniocerebral war wounds. The number of cases of traumatic insanity or epilepsy, or of cases of tumor of the brain which develop following such injuries, is surprisingly small.

CONCLUSIONS

Deep traumatic petechiae are dependent chiefly on the effects of vasomotor concussion, causing vasodilatation, prestasis, anoxemia, impairment of the walls of the vessels, diapedesis and perivascular hemorrhage.

Tearing of the vessels was rarely observed in relationship to perivascular petechiae.

Fresh petechiae were observed in cases of the longer periods of survival. An explanation of their mechanism is offered.

Ring hemorrhages are produced by prestatic diapedesis, followed by stasis.

Petechiae were frequent in the cerebral white matter, the central gray matter and the brain stem; they were less frequent subtentorially and were rare in the cerebral cortex. They were frequent about the arterioles and infrequent about the capillaries.

Thrombotic and hyaline changes in the vessels were frequent and were ascribed to the effects of concussion.

The effects of severe concussion may explain late petechial hemorrhages, late apoplexy and softening due to irreversible cerebral vasomotor involvement and consequent progressive pathologic changes in the blood vessels and cerebral circulation.

Deep traumatic petechiae in cases of trauma to the head are essentially concussion phenomena and serve as a point of anatomic differentiation of concussion and contusion.

DISCUSSION

Dr. Stanley Cobb, Boston: The great increase in the number of cerebral injuries is appalling. It is due principally to the increasing number of motor vehicles which swarm on the highways at ever increasing speed. If an epidemic of encephalitis killed twenty or thirty thousand people in the United States in one year, the medical profession, the Public Health Service and all available agencies would be mobilized to combat the pest. Yet nothing is done about this dreadful scourge injury due to automobile accidents. Physicians should organize and report every reckless driver, as they should report every typhoid carrier.

This paper is important because it strikes directly at the heart of the question by asking what causes the common lesion, the deep petechial hemorrhage. The eight patients fall into three groups: those who lived from three to eight days after the trauma (patients 1, 7 and 11), those who lived from one to thirteen hours after trauma (patients 5, 10 and 2) and those who died "immediately." One would expect the lesions in these three groups to be different, but they differed but little. True, the patients who lived several days showed more thrombi, infarcts and ring and ball hemorrhages. But all showed the deep perivascular hemorrhages in the white matter and the basal ganglia, even if they died "immediately." In all cases there were scattered local lesions. This indicates to me that "death" was not "immediate."

The authors should be asked to define these two terms.

Experiments of mine have shown that cutting off cerebral circulation for from six to eight minutes causes damage to cells if the animal survives even fifteen minutes thereafter; no hemorrhages, however, occur. In other words, immediate death (meaning cessation of the heart beat) would cause complete stasis of the entire circulation, and no tissue reaction would occur, merely postmortem changes. It is my contention, therefore, that these patients did not die immediately and that a few minutes of life is sufficient to cause these focal lesions.

One thinks of three possible causes of the petechial hemorrhages: 1. Mechanical waves causing rupture of vessels. This seems to be ruled out by the authors' careful histologic examination by serial section. 2. Vasomotor paralysis from shock, causing stasis. This is possible, but when one considers what a feeble vasomotor mechanism the brain possesses, the explanation seems dubious. Forbes has shown that vasoconstriction in the brain is only about one-tenth as active as in the skin. 3. Acute swelling of the oligodendroglia cells. This was not especially looked for in these brains, but in almost every case there was noticed "vacuolation" or "honeycombing." This might well be due to acute swelling. Special stains for oligodendroglia should be made on brains fixed especially within a few hours. In most of these cases necropsy was performed too late.

I agree with the authors that asphyxia of the cerebral tissue is probably a cause of the late lesions, especially anoxemia of the vessel walls, with resulting diapedesis. I agree with them that stasis of the blood stream is an important pathologic event. I have shown in a paper written in collaboration with Hubbard in 1927 that stasis of the pial veins can cause "ring hemorrhages" in the deep cerebral tissue. I should like to ask whether special stains for oligodendroglia were used. If not, I feel that a combination of acute glial swelling and vasomotor paralysis causes the local anoxemia necessary to allow diapedesis and the formation of perivascular petechiae.

I should like to emphasize also that this work illustrates again the uselessness of the term "organic" and "functional." The line between them is impossible to draw, and the belief in such a line is naive. As Jelliffe long ago pointed out, the issue is this: Is the lesion reversible or irreversible? In other words, can it heal and leave no lesions, at least no lesion demonstrable by the methods of 1936?

DR. LEO ALEXANDER, Boston: I am greatly impressed by this contribution by Dr. Schaller and his co-workers. I have seen the slides illustrating a number of his cases. My associates and I have seen and preserved specimens with a fair number of similar hemorrhages in the central white matter of the brain. At the Boston City Hospital Dr. Leary, Dr. Cobb and Dr. Putnam have frequently called attention to the fact that these posttraumatic lesions exist. This problem has great importance from many points of view. From the standpoint of legal medicine it

is important to know that in certain cases of trauma there is no evidence of a direct continuative trauma from the skull to the brain. The regions affected are often far from the site of the direct external trauma. There are still certain workers who would prefer in such cases to consider the lesions as due to a spontaneous encephalitic or toxic process rather than as a definite traumatic disease. Dr. Schaller has contributed a great service in demonstrating the frequency of these posttraumatic lesions.

As to the mechanism, I can add little to what Dr. Schaller and Dr. Cobb have said. There is, however, another point of view to be contributed. There is a possibility that the intimal tears may be due to the circulatory impact, especially on the venous side. My associates and I have observed a great number of venous hemorrhages in our cases. After the intimal tear platelets may settle and form a thrombus. This may explain the free interval which occurs frequently in these cases.

One of our patients was lucid for about an hour after the injury, when he suddenly lost consciousness and remained in a stuporous condition a week after the onset of the stupor, until his death. This probably was due to the fact that thrombi were slowly forming in the injured veins. Whether these veins were injured by stasis or by intimal tearing is hard to decide. We are working on the elucidation of this question now.

In one of our cases, that of a man who survived injury for eight days and was in deep stupor all that time, necropsy revealed perivenous necroses with rather sharply outlined, plaquelike areas of demyelinization, which resembled plaques of multiple sclerosis. In the light of Dr. Putnam's observations, this analogy is of interest and may serve to explain the pathogenesis of demyelinization in both these conditions.

Dr. Andrew H. Woods, Iowa City: I was able to observe three cases of trauma to the spinal cord, with fatal outcome, that are of interest and bear on the theory that has just been propounded. In two of these cases the missiles, bullets, did not touch the dura but struck the upper thoracic vertebrae: In one case the spine was struck and in one the transverse process. In a third case, in which the cervical part of the spinal cord was involved, the bullet struck the outside of the dura but did not penetrate it. I studied all three cases at autopsy. By taking sections from about 2 cm. above to 2 cm. below the point of impact, I was able to see these petechial hemorrhages which were mostly nearest the point where the missile struck and became gradually fewer centrifugally.

The dura mater is a resistant tube filled with practically fluid contents, the pia mater and spinal cord being semifluid. Through this enclosed mass the blood vessels run. If a tube of water is struck tangentially, the lines of conduction of the force spread from the point of impact along the radii of the hemisphere, with the point as a center. Blood enclosed in the vessels cannot be driven radially but is forced onward within the caliber of the vessels, the driving force being relatively tremendous near the point of impact. The effect on any vessel would be as though, when it was attached to a syringe, fluid were abruptly driven into it by a sudden pressure of the piston. In the cases cited the vessels appeared to be dilated, and the impression on me was that, as Dr. Schaller has mentioned, these vessels had been suddenly overstretched, "irrecoverably dilated." There was no sign of gross rupture. Dr. Schaller's explanation of this extrusion of red and white cells as being due to an ensuing diapedesis through biologically damaged walls appears to me sound.

It is interesting to study the cases in which the spinal cord is involved, for the areas affected are limited and the regions in which the force operated can be studied more satisfactorily. To follow this hydrodynamic principle in the cases of intracranial trauma brings one up against more complicated conditions affecting the distribution of forces, but it is probable that overstretching, at times even with rupture, of vessel walls, in the way that it appeared in these cases in which the spinal cord was involved, is of equal importance in the brain.

DR. WALTER FREEMAN, Washington, D. C.: Did I understand Dr. Schaller correctly as saying that exactly the same phenomena were observed in the cases in which death occurred immediately as in those in which death occurred somewhat later? Would not the occurrence of ring hemorrhages and petechial spots immediately after the injury indicate a direct action on the blood vessels, even though the trauma, the tear in the vessels, was not demonstrable?

DR. ADOLF MEYER, Baltimore: These minute hemorrhages played a rather interesting rôle in the first attempts to explain shell shock. As some may remember, the whole British interpretation of shell shock was at first rather unhappily influenced by the conception of Frederick Mott, who thought it to be a structural process, and undoubtedly the question might easily have arisen, particularly in cases in which an inaccurate history was obtained as to how many symptoms might have been due to trauma and how many might be incidental to the unusual strains.

Similar conditions and difficulties occur with convulsive attacks. One also has to recognize that injuries do not always present themselves as perceptible and localizable.

I should like especially to know whether Dr. Schaller has made an effort to determine whether these small hemorrhages were not more or less limited to regions which were exposed to the resistant membranes, to the falx (bruising the callosum) and to parts which in themselves do not show any glaring macroscopic contusions from the outside. Dr. Bagley published cases in which there were few massive hemorrhagic conditions but a great many smaller hemorrhages which might easily be due to direct traumatic injury by the dura, sometimes together with more obvious ruptures but sometimes with the kind of condition that Dr. Woods and others undoubtedly have noticed and which may be due, as Dr. Freeman has said, to traumatic influences in which the protective functions that are normally exerted by the dura act to disadvantage.

DR. WALTER F. SCHALLER, San Francisco: This discussion has been valuable for future work that we propose to do with controlled experiments on animals. I was somewhat hesitant to report on our work at this stage. When Dr. Cobb was in California I told him that the study of the nerve elements was incomplete. He replied, "Sometimes it is well to close one's eyes and go ahead." So I closed my eyes and went ahead.

The point is well taken that the vasomotor supply of the brain may not be comparable with that in the ear or the mensentery of the rabbit. However, if spasms in vessels of the brain produce important functional effects, paralytic effects may produce similar effects.

One cannot definitely state that some of the hemorrhages considered to be due to diapedesis are not caused by rhexis; I suppose that they are. Exceedingly thin serial sections would be necessary to rule out tears in the sense of Cassasa. On the other hand, our work appears to demonstrate that there are far more hemorrhages caused by diapedesis than by rhexis.

Defects which we considered to be edematous might well have been due to swelling of unstained glial elements. It seems reasonable that large hemorrhages

outside the perivascular space involving the parenchyma may produce permanent damage of essential nerve elements.

In answer to Dr. Freeman: In the cases of longer standing, in which the patients died after three and one-half days, four days and eight days, respectively, I observed, in addition to ring hemorrhages, perivascular fresh petechiae, thereby indicating a progressive condition from prestasis to total stasis.

In reply to Dr. Meyer: Dr. Courville, of Los Angeles, has studied the regional occurrence of petechiae with reference to the direction and amount of traumatic force, which I have not done. I think that this is important. The mechanism of injury in the patient with petechiae in the callosum, who died after eight days, may have been that which Dr. Meyer suggested.

CONTRIBUTION MADE BY ROENTGENOGRAPHIC EVIDENCE AFTER THE INJECTION OF IODIZED OIL

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NEW YORK

Spinal iodolography, or myelography accomplished by the injection of iodized oil into the spinal canal, had its inception only fourteen years ago.[1] During the first seven years it became an exceedingly popular procedure in the diagnosis of lesions of the spinal cord. Reports in increasing numbers began to appear in the medical literature, recording favorably the results of the procedure. There appeared few warnings as to immediate complications and latent sequelae resulting from the method (Ayer and Mixter,[2] Nonne,[3] Lindblom,[4] Sharpe and Peterson,[5] Maclaire,[6] Craig,[7] and Ebaugh and Mella[8]). This diagnostic method continued to gain favor with neurologists and neurosurgeons until 1929, when a paper appeared in which Davis and his co-workers[9]

From the Neurological Service of the Mount Sinai Hospital.

Read at the Sixty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 1, 1936.

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8. Ebaugh, F. G., and Mella, H.: Lipiodol in Localization of Spinal Lesions: The Local and Systemic Effects of the Injection of Lipiodol into the Subarachnoid Space, Am. J. M. Sc. **172**:117, 1926.

9. Davis, L.; Haven, H. A., and Stone, T. T.: The Effect of Injections of Iodized Oil in the Spinal Subarachnoid Space, J. A. M. A. **94**:772 (March 15) 1930.

reported profound alterations in the leptomeninges of dogs, presumably caused by the irritating effect of iodized oil injected into the spinal subarachnoid space. They assumed that a similar condition prevails also in human subjects who receive intraspinal injections of iodized oil and concluded that the advantages of injections of iodized oil were insufficient to counterbalance the deleterious effect on the coverings of the spinal cord.

The appearance of this report marked the beginning of a sharp decline in the number of papers dealing with intraspinal injections of iodized oil. The impression is gained that this decline reflects the disfavor into which the method had fallen and the infrequency with which iodized oil is now used in myelography. However, the procedure is not completely abandoned, and reports, although less frequent, still stress its usefulness. The observations made by my colleagues and me, which fail to corroborate the experimental evidence of Davis and his co-workers on the toxicity of iodized poppy-seed oil, point to distinct diagnostic gains that are attained by the method. Since our conclusions are based on ample and thoroughly studied material, they deserve serious consideration.

In evaluating the experience gained from the study of our material, an attempt was made to give unbiased and accurate answers to the following questions: 1. Is iodized oil of the type we have used (iodized poppy-seed oil) likely to give rise to disturbing symptoms or signs immediately after the injection? 2. Have sequelae appeared at any time—days, months or years after the injection of iodized oil into the subarachnoid space? 3. Were histologic changes detected in the meninges and spinal cords of patients who were subjected to injections of iodized poppy-seed oil into the subarachnoid space? 4. What are the indications for the use of iodized oil in disease of the spinal cord, or what advantages are offered by this method that cannot be procured from any other available diagnostic means?

The answers to these questions are based on a survey of one hundred and thirty-eight cases in which intraspinal injections of iodized poppy-seed oil were made. The accompanying table shows the final diagnosis in the cases, with the aids constituting the material for this study.

In only two of the total one hundred and thirty-eight cases were there reactions of relative severity immediately following the injection. In one case there was a transient vasomotor disturbance, from which the patient recovered in the course of several minutes. It was attributed not to the medium injected but to the probable effect of the cisternal puncture. In the other case there was a somewhat protracted period of pain along the spine and in both shoulders. In a few instances there was a mild transient headache or slight elevation of temperature (about 1 F.).

For the purpose of establishing or excluding the probable latent effect of iodized oil, a large number of patients were invited at various times to return for reexamination. Sixty-five patients responded, some

Comparative Values of Evidence from Iodolography and Manometric Tests in a Series of One Hundred and Thirty-Eight Cases *

Final Diagnosis	Total Number of Cases	Diagnosis Verified by		Manometric Tests				Injection of Iodized Poppy-Seed Oil			
		Laminectomy	Subsequent Course	Complete Block	Partial Block	No Block	Xanthochromia	Complete Block	Partial Block	Small Globules†	No Block
Extramedullary (intrameningeal) tumor	20	19	0	2	9	3	6	14	4	0	2
Intramedullary tumor or syringomyelia	12	5	7	2	4	6	2	5	2	0	3
Primary extradural tumor	6	6	0	3	2	1	1	1	2	0	0
Metastatic tumors (multiple)	6	2	2	2	1	0	0	2	1	0	0
Multiple angiomas	2	0	2	0	1	1	0	0	0	1	1
Compression of the cord	3	2	1	0	3	0	1	2	1	0	0
Varicosities of the cord	1	1	0	0	1	0	0	0	0	0	1
Arachnoiditis	18	8	9	2	6	9	0	5	3	8	2
Radiculitis	18	3	15	0	3	16	0	0	1	4	13
Meningomyelitis syphilitica	4	0	4	0	3	1	0	0	0	3	1
Infectious meningomyelitis	7	1	3	0	4	3	0	0	0	2	5
Intramedullary disease of the cord of undetermined type	10	2	8	3	3	6	0	0	0	4	6
Diffuse degenerative disease	5	0	5	0	0	5	0	0	0	0	5
Combined sclerosis	1	0	1	0	1	0	0	0	0	0	1
Multiple sclerosis	12	2	10	0	4	8	0	0	0	9	3
Amyotrophic lateral sclerosis	5	0	5	0	3	2	0	0	0	0	5
Lateral sclerosis	2	0	2	0	0	0	0	0	2 Transient	0	0
Spondylitis	3	0	3	0	1	2	0	0	0	0	3
Spina bifida occulta	1	1	0	1	0	0	0	0	1	0	0
Tumor of the parietal lobe	1	1	0	0	0	1	0	0	0	0	1
Psychoneurosis	1	0	1	0	1	0	0	0	0	0	1

* The table, in addition to listing the types of cases in which studies were made with iodized oil, discloses some other interesting data: the frequency with which iodolography indicated the presence of a block when manometric readings failed to disclose it; the infrequency of xanthochromia in instances in which iodolography established the existence of a block, and the presence of multiple small collections of iodized oil at various levels in instances of arachnitis and meningomyelitis.

† Small globules of oil irregularly distributed at various levels.

appearing several months and others several years (from two to four years) after the injection of iodized poppy-seed oil. In one instance the patient carried the oil in the subarachnoid sac for about ten years.

All the patients were questioned in detail as to the probable appearance of signs of meningeal irritation and were given a thorough neurologic survey.

In none of the cases but one in which reexamination was thus made were there subjective complaints or objective findings which could be regarded as the aftermath of the injection of iodized oil. In one instance the patient complained of accentuation of pain in the back. In thirty-four of the cases roentgenograms were again taken to determine whether the oil was reabsorbed to any degree or had become encapsulated, as has been claimed by some observers. No appreciable reduction in the mass of iodized oil was noted, and on placing the patients in the Trendelenburg position it was found with the aid of the fluoroscope that the iodized oil moved toward the dorsal region. In three instances, the patients having died in the hospital, the meninges and spinal cords became available for histologic study. No evidence of leptomeningitis was observed. Thus, it may be concluded that iodized oil has no deleterious effect on the leptomeninges in man, and aside from the hazards of cisternal puncture its use is not likely to give rise to immediate or delayed disturbances.

The employment of iodized oil in the cases in our series was dictated by a wide range of circumstances. It was resorted to when signs and symptoms of disease of the spinal cord indicated with fair certainty the presence of an intraspinal tumor, although the sensory level was not sufficiently definite and the manometric readings were unconvincing. In such cases the injection of iodized oil gave highly gratifying results, as the level of obstruction was then established with seldom failing accuracy.

Iodized oil was also used when the diagnosis of an expanding lesion was certain but it was difficult to say whether it was intramedullary or extramedullary. The myelograms in these cases have in some instances, by presenting fairly characteristic shadows, provided a useful guide for differential diagnosis.

Iodolography was of particular service when it was essential to identify the existence of a tumor below the level of the lumbar segment at which a lumbar puncture is usually performed. Obviously, in such instances manometric readings would be valueless, and roentgenography with the use of iodized oil was the method of choice in establishing or excluding the presence of an expanding lesion in the region of the cauda equina.

Iodolography was found useful at times in recognizing the metastatic character of an expanding lesion, by demonstrating the existence of several levels of obstruction.

Iodized oil was also useful in instances in which the differential diagnosis of a tumor of the spinal cord and an obstructive lesion of

inflammatory character was difficult. This was particularly true when the condition known as arachnoiditis was encountered. By virtue of large pockets of arrested cerebrospinal fluid it often gives rise to signs and symptoms not unlike those of an expanding neoplastic intraspinal lesion. Iodized oil, with its diagnostic shadows, helped to exclude the existence of an expanding lesion. By demonstrating several sites of partial obstruction it aided in the recognition of the true character of the disease process. It also helped to identify the point of maximum block, which was of great service when surgical intervention was decided on.

Iodized oil was also used in conditions in which a degenerative disease of the cord, such as multiple sclerosis, combined sclerosis or amyotrophic lateral sclerosis, was considered as the most probable disease process but in which, in view of the existence of a vague sensory level, a partial block or atypical manifestations, the exclusion of an expanding or obstructive lesion on the basis of clinical observations alone was difficult; under these circumstances normal findings with iodized oil helped in reaching a final diagnosis and at times obviated the necessity of a projected exploratory laminectomy.

SUMMARY

The advantages of myelography with the use of iodized oil may be summarized as follows: It helps in the majority of instances to establish the exact level of compression of the spinal cord with a certainty greater than is offered by other methods. It often helps to distinguish an extramedullary from an intramedullary tumor. By disclosing the presence of several blocks at several levels, it assists in identifying the metastatic character of a compressing lesion. It is of service in recognizing obscure obstructive lesions, such as arachnoditis. It is of valuable assistance in differentiating neoplasms of the cauda equina from lesions simulating them, such as lumbosacral radiculitis. It aids in the identification of obscure anomalies of the spinal column, such as spina bifida occulta, particularly when accompanied by changes in the enclosed structures. It is no less helpful in excluding the existence of tumor of the spinal cord in instances of atypical inflammatory or degenerative disease of the spinal cord.

The patient, while not subjected to unjustified hazards, shares in all the diagnostic advantages offered by this method. Aiding in the early recognition of the lesion and the accurate identification of its site, idolography leads to direct and often beneficial therapeutic measures. No less important is the fact that by guiding the surgeon to the precise level it spares the patient one or more laminae. By excluding

the existence of a neoplasm it often saves the patient from the hazards of an unnecessary laminectomy.

It may be added, however, that, whatever its advantages, iodolography should be regarded merely as a useful diagnostic procedure, highly valuable when used judiciously with other fully established methods of neurologic investigation.

NEUROPTIC MYELITIS VERSUS MULTIPLE SCLEROSIS

A PATHOLOGIC STUDY

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A combined lesion of the spinal cord and the optic nerve fibers is not uncommon. It occurs in multiple sclerosis, cerebrospinal syphilis, disseminated tumors of the central nervous system, encephalomyelitis, septicopyemia and so-called neuroptic myelitis (Devic's [1] disease). Of the foregoing conditions, neuroptic myelitis has attracted a great deal of attention of late, and, as it usually runs an acute or subacute course (from two months to one year), it is often designated as acute multiple sclerosis or disseminated encephalomyelitis. For this reason it is generally not considered a specific disease process, though some (Michaux,[2] Sager and Grigoresco,[3] Merkel,[4] Delbeke and van Bogaert [5]) view it as a well defined clinical entity, different from acute disseminated encephalomyelitis or so-called acute multiple sclerosis. The results of histopathologic study of a case seem to favor the latter view, that neuroptic myelitis is a well defined clinical syndrome with definite clinical features. It belongs with the group of what has been described [6] as multiple degenerative softening of the central nervous system with changes prevalent in the spinal cord.

From the Division of Neuropathology, University of Illinois College of Medicine.

Read by title at the Sixty-Second Meeting of the American Neurological Association, Atlantic City, N. J., June 2, 1936.

1. Devic: Myélite subaiguë compliquée de névrite optique, Bull. méd. **8**: 1033 (Nov.) 1894.

2. Michaux, L.: La neuro-myélite optique aiguë, Paris, Louis Arnette, 1930.

3. Sager, O., and Grigoresco, D.: Beiträge zum Studium der Ophthalmoneuromyelitis und ihrer Beziehungen zur disseminierten Encephalomyelitis, Arch. f. Psychiat. **98**:378, 1932.

4. Merkel, K.: Ueber einen Fall sogenannter Neuromyelitis optica, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:591, 1930.

5. Delbeke, R., and van Bogaert, L.: L'encéphalomyélite disséminée aiguë, J. de neurol. et de psychiat. **31**:645, 1931.

6. Hassin, George B., and Bassoe, Peter: Multiple Degenerative Softening Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:613 (May) 1922.

REPORT OF A CASE

A white woman aged 33 was admitted to the Cook County Hospital on Oct. 5, 1933, because of blindness, paralysis of the lower extremities, weakness and numbness of the upper extremities and disturbances of the bladder and rectum.

History.—In August 1932 (the exact date was not given) the patient suddenly experienced shooting pains and weakness, with numbness in the right leg. The weakness and numbness extended first to the opposite lower extremity and later upward, reaching a line between the navel and the breast. With the appearance of the numbness the pain in the legs disappeared, but there were for some time various abnormal, some painful, sensations in the lower extremities, which grew weak and finally became paralyzed. The condition improved somewhat about three months after the onset of the disease, when strength in the legs gradually returned and the patient was able to move about. In May 1933, after an attack of "influenza" of three weeks' duration, the old complaints recurred—there were complete paralysis of the lower extremities, anesthesia up to the level of the umbilicus and urinary disturbances. The emptying of the bladder became automatic and remained so. The upper portion of the body, the arms, the cranial nerves and the vision were not affected until thirteen months later, at the end of September 1933, about five days before her admission to the hospital. She experienced pain and itching in the right upper extremity, which soon became paralyzed, and visual disturbances appeared. Objects, according to information given by the patient (which is not altogether reliable) were much better perceived when held to the left (right ?) than when held to the right (left ?) side of the body. The bladder emptied itself automatically, as she had no desire to urinate, and the bowels were constipated.

The previous history, except for the usual diseases of childhood, was without significance. There had been no venereal disease.

Examination.—The patient was poorly nourished and unable to move her lower extremities, which were spastic, flexed and adducted. The upper extremities were also spastic but could be moved slightly.

Reflexes: The patellar, biceps and triceps reflexes were lively (4+); the ankle jerks could not be elicited; the plantar, abdominal, pharyngeal and corneal reflexes were all present, and pathologic reflexes (Babinski, Rossolimo and Hoffmann) were absent.

The cranial nerves were normal. Nystagmus was absent, and the fundi of the eyes, examined on October 5, presented a mild pallor in the inferior temporal sector of the right eye and slight blurring of the left disk. The patient at the time of this examination could not discern light from darkness with the left eye; she was able to see movements of the hands with the right eye. The pupillary reaction could not be ascertained, as the pupils had been dilated with atropine.

Course.—The tendon reflexes, including the patellar reflex, disappeared; vision grew steadily worse; objects were perceived dimly; bed sores developed in the lower part of the back, and severe pain was felt in the arm, which often necessitated the administration of morphine. The patient was restless, irrational most of the time and unable to swallow. During her stay in the hospital the temperature, which on her admission was 98.8 F., became elevated, ranging from 102 to 108.2 F. (before death on Oct. 20, 1933, fourteen months after the onset of illness). The pulse rate ranged between 112 and 120, and the respiratory rate ranged between 20 and 28. The blood pressure was 120 systolic and 90 diastolic.

A diagnosis of neuroptic myelitis was made on the basis of the blindness and the clinical picture of a lesion of the spinal cord: sudden spastic paraplegia preceded by severe pain in the legs and associated with complete anesthesia and disturbances of the rectal and bladder sphincters.

Necropsy (Dr. R. H. Jaffé).—The essential findings were catarrhal suppurative cystitis; bilateral pyelitis, subacute infectious hyperplasia of the spleen, anemia and parenchymatous degeneration of the myocardium; ancient bilateral salpingectomy and oophorectomy; nodose goiter, and extensive decubitus ulcers. The spinal cord was moist and soft and showed lack of demarcation between the gray and the white substance.

Microscopic Observations: Sections of the spinal cord stained by Kultschitzky's modification of the Weigert-Pal method exhibited scattered patches of demyelinization which, as in multiple sclerosis, irregularly covered both the white and

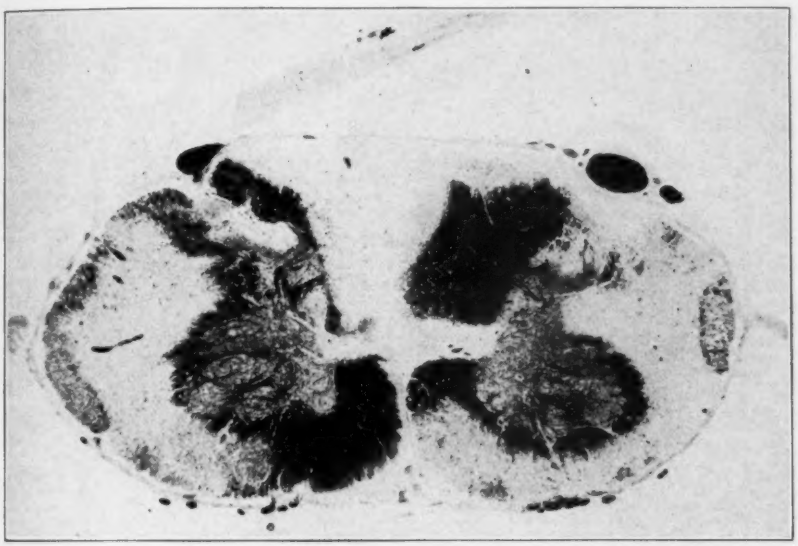

Fig. 1.—Neuroptic myelitis. A section from the cervical region prepared with the Kultschitzky stain.

the gray substance (fig. 1). They were particularly marked in the cervical region, where only remnants of healthy tissue were left (in the anterior and the posterolateral columns). The spinocerebellar tracts were fairly well preserved in the left half, and only small fragments of them were present on the right side. The gray substance was especially affected at the base of the right posterior horn, where a portion of the anterior horn and the commissure also appeared completely demyelinated. The destruction in the thoracic region was much more extensive (fig. 2). Here the entire cross-section appeared almost equally demyelinated, and only a small patch of the white substance remained somewhat preserved. The best preserved segments were in the lumbosacral region where patches of demyelinization were scarce, being confined to the posterior and partly to the lateral columns. Definite signs of secondary degeneration could not be made out.

Stained with toluidine blue, the patches of demyelinization exhibited great cellularity (fig. 3). They were irregular, extending digit-like into both the gray and the white substance, and were densely covered with nuclei, which were mostly irregular and polymorphous. The invading cells were astrocytes, oligodendrocytes, microglia cells and gitter cells. In some areas one type of cells predominated; in others all the aforementioned types were equally represented. The prevalence of some type of cells reflected on the stainability of the section (as noted by Alajouanine and his co-workers [7]). For instance, areas which stained darker with toluidine blue consisted for the most part of gitter cells, while areas that appeared light consisted mainly of astrocytes or microglia cells. Astrocytes, however, were much scarcer than microglia cells or gitter cells and were usually present in the marginal areas of the patches bordering on the white substance of the spinal cord. Fibrillary astrocytes were even rarer than cytoplasmic astro-

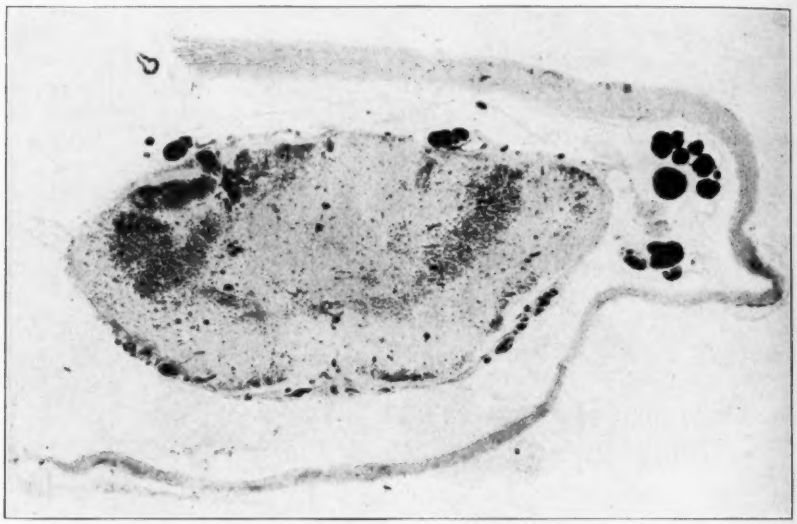

Fig. 2.—Neuroptic myelitis. A section from the thoracic region prepared with the Kultschitzky stain.

cytes and their fibers (glia fibers) were often broken up into small quadrangular or rounded fragments (fig. 4), described by Alzheimer as filling bodies and by Cajal as clasmatodendrosis. In some places, the filling bodies were intimately mixed with gitter cells, a phenomenon entirely foreign to multiple sclerosis. The changes in the glia fibers described could be brought out especially well in longitudinal sections of the spinal cord. They were present in both the gray and the white substance, where they crowded the spaces among the nerve fibers and contained in their midst numerous gliogenous gitter cells. In other sections the gitter cells were arranged in longitudinal rows, each row of cells divided from the others by glia fibers and replacing degenerated nerve fibers, without regard

7. Alajouanine, T.; Hornet, T.; Thurel, R., and Rossano, R.: Un cas anatomoclinique de sclérose en plaques aiguë avec symptomatologie de neuropticomyélite, Rev. neurol. **64**:98, 1935.

for the territorial blood supply. This suggests, as emphasized elsewhere,[8] the gliogenous and not the microglial origin of the gitter cells. Such a view is also sustained by the presence of myelophages, which were especially common in areas that were less damaged. For instance, in the lumbar region of the spinal cord, where the posterior columns were mainly affected, numerous gitter cells were present, mixed with occasional cystoplasmic glia cells and many myelophages, which harbored broken-up nerve tissue within their large vacuoles. In the ventral spinal columns, which grossly appeared normal and were not very cellular, the predominating cells were cytoplasmic astrocytes intermingled with microgliocytes and oligodendrocytes. The latter, as a rule, did not appear swollen, but exhibited only some nuclear changes. The nuclei were irregular and shrunken and contained chromatin in the form of a few densely stained granules arranged along the membranes ((karyorrhexis). The microglia cells appeared as rod cells (fig. 5) and

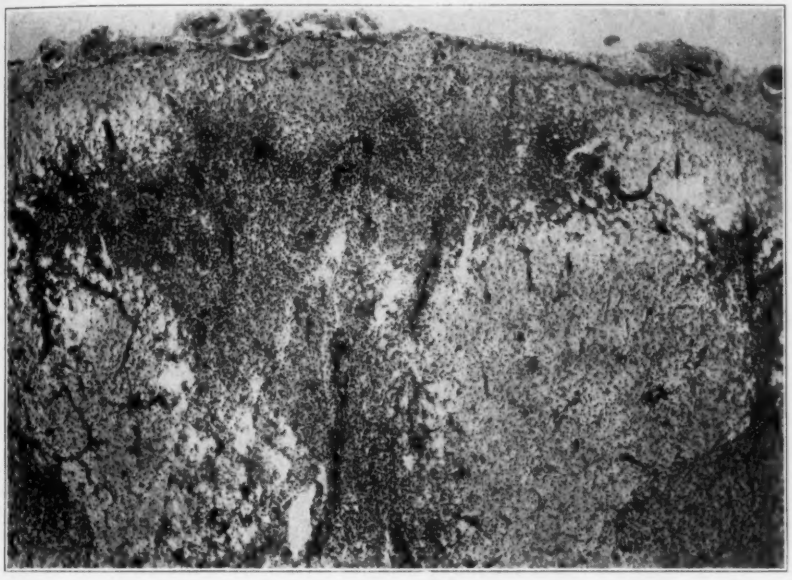

Fig. 3.—Marked cellular infiltrations of the posterior columns of the spinal cord. Toluidine blue stain; × 41,

were exceedingly numerous. Under a higher power lens it was possible to demonstrate in them divided and subdivided polar processes, which gave the cell body an appearance of a typical microglia cell. Their nuclei, like those of the gitter cells and the oligodendrocytes and cytoplasmic astrocytes, presented the most bizarre forms. They appeared bean shaped or kidney shaped or as dumb-bells. Nowhere did the microglia exhibit transitional forms suggestive of the formation of gitter cells.

The nerve fibers, in areas slightly damaged, usually exhibited tumefied myelin and axons, minute fragments of myelin and reactive glial changes, but they showed

8. Hassin, George B.: Reacting Cells in the Brain in the Presence of a Foreign Body, Arch. Neurol. & Psychiat. **36**:231 (Aug.) 1936.

no changes in the parts of the spinal cord preserved. The blood vessels were generally patent; the cells of their tunics were well formed. Their nuclei were rich in chromatin and exhibited a variety of forms that defied detailed description. The majority were proliferated endothelial and adventitial cells (fibroblasts), and there were also many newly formed capillaries represented by endothelial buddings. Smaller blood vessels harbored in their distended perivascular spaces immense masses of gitter cells, which were occasionally mixed with lymphocytes.

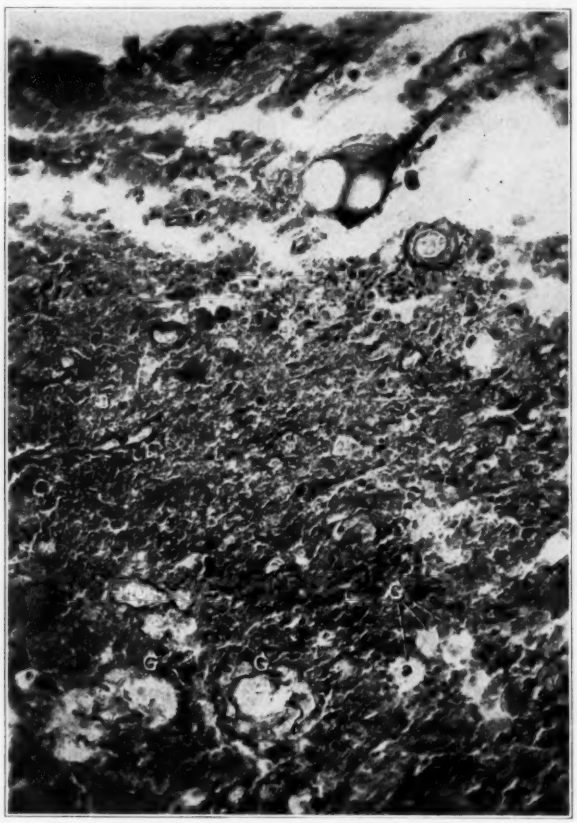

Fig. 4.—A vacuolated and expanded ganglion cell is shown in the upper part of the photograph. The rest of the picture consists of minute bodies (filling bodies) mixed with gitter cells (*G*). Alzheimer-Mann stain; × 370.

As has been noted, the great cellularity of the parenchyma was present in both the gray and the white substance but was more marked in the former. It was always associated with changes in the ganglion cells of the anterior and posterior cornua, extending throughout the spinal cord, in some segments more, in others less marked. The changes varied from mild chromatolysis and swelling of the cell bodies in the sacral region to vacuolation (fig. 4) and complete disintegration in the dorsal and cervical segments. In areas of far gone destruction, the dorsal area, for instance, the ganglion cells were enormously tumefied and devoid of dendrites and Nissl bodies, of which only remnants were left, while

the nuclei were in a state of karyorrhexis. In some thoracic segments the ganglion cells were so sparse and pale that they could not be detected even after careful search. In such areas, which were apparently devoid of ganglion cells (fig. 6), the white matter could not be differentiated from the gray substance. The cells that could be made out with a high power lens were homogeneous; their dendrites were swollen and, like their bodies, were sometimes shrunken, the nuclei containing only a few granules of chromatin. Practically all such changed ganglion

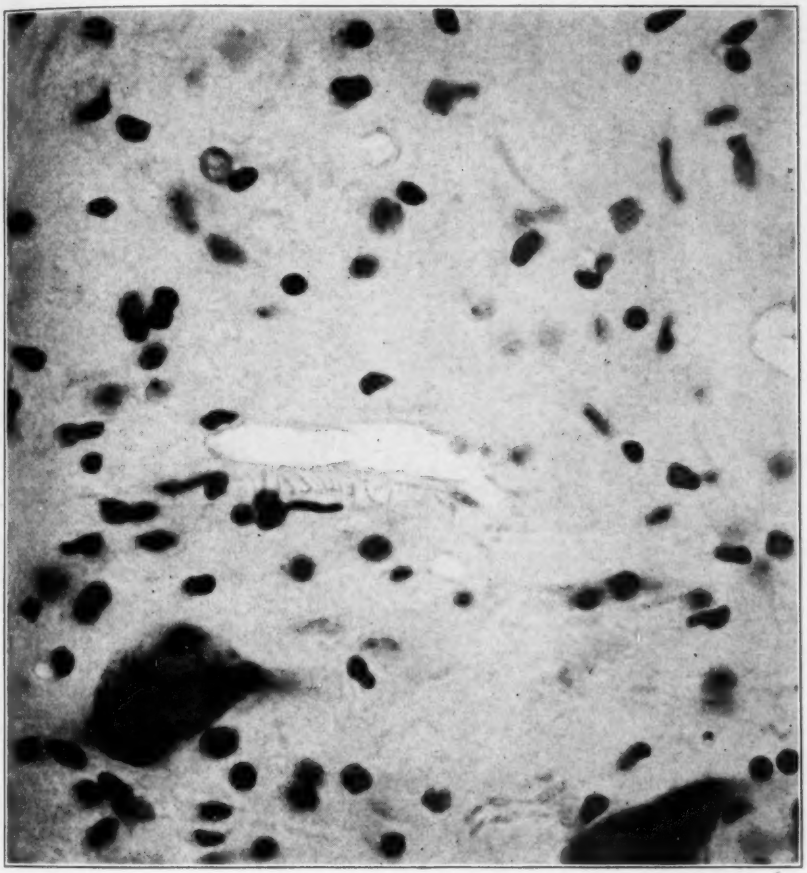

Fig. 5.—Neuroptic myelitis. Many rod cells and other cell bodies in a well preserved segment of the spinal cord. Toluidine blue stain; × 700.

cells exhibited neuronophagia and satellitosis and appeared as though bathed in immense masses of nuclei of various shapes, forms and sizes. It is rather strange that no microglia cells were encountered within the nuclear masses, though neuronophages could be made out to be microglia cells at some levels. The cell destruction and the density of the nuclear invasion ran parallel, both evidently having been caused by the same destructive agent, which, as has been noted, affected the gray and the white substance alike.

Changes in the Optic Tract and the Brain: The right optic tract (the left optic nerve and external geniculate bodies could not be studied) and occipital region (cuneus) exhibited definite changes in the form of foci of gitter cells, microglia cells and glia cells (figs. 7 and 8). Axons were only occasionally encountered, as the majority of the nerve fibers were destroyed. On the whole, the changes resembled the dense foci of the spinal cord already described (repro-

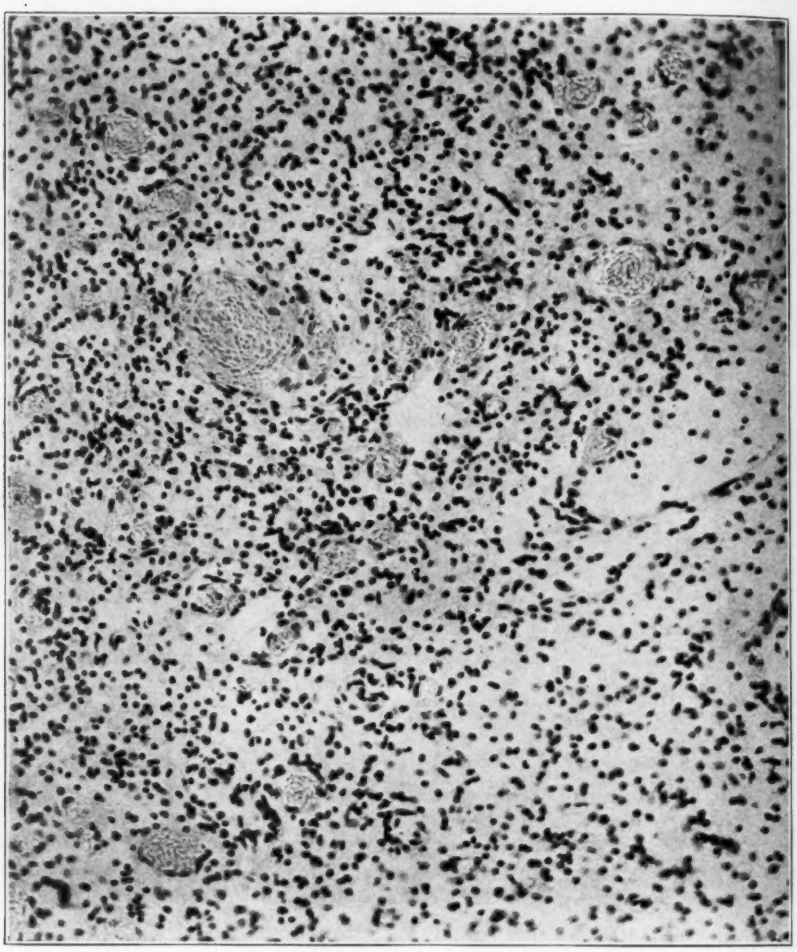

Fig. 6.—Neuroptic myelitis. A section from the dorsal region showing marked cellularity of the anterior horns, numerous hyperemic blood vessels and absence of ganglion cells. The invading cells are mostly rod cells (microglia). The picture should be compared with figure 10. Toluidine blue stain; × 190.

duced in figures 3 and 4). The majority of the cell elements of the foci were gitter cells, mixed with myelophages and some cytoplasmic and fibrillary astrocytes. The blood vessels were prominent; their walls contained hypertrophied endothelial cells, and the adventitia was densely infiltrated with gitter cells. The

focus in the cuneus did not reach the cortical layers (figs. 8 and 9), which, however, exhibited changes. There were in the latter many cytoplasmic astrocytes; the ganglion cells were pale and stained badly, and the nuclei appeared colorless, homogeneous and entirely deprived of chromatin (karyolysis). The large pyramidal cells, which were fairly well preserved, stained better; but some cells were vacuolated as if eaten away, and their nuclei exhibited a scarcity of chromatin. Satellitosis was rare, and neuronophagia was not noted at all. Myelinated fibers, both tangential and radial, were sparse. In the rest of the cortex, brain stem and cerebellum the ganglion cells were practically normal. The only anomaly in these regions was two punctate foci of softening in the posterior limb of the right internal capsule and an apparent increase of rod cells. No changes were found in the cuneus of the opposite left occipital lobe, which

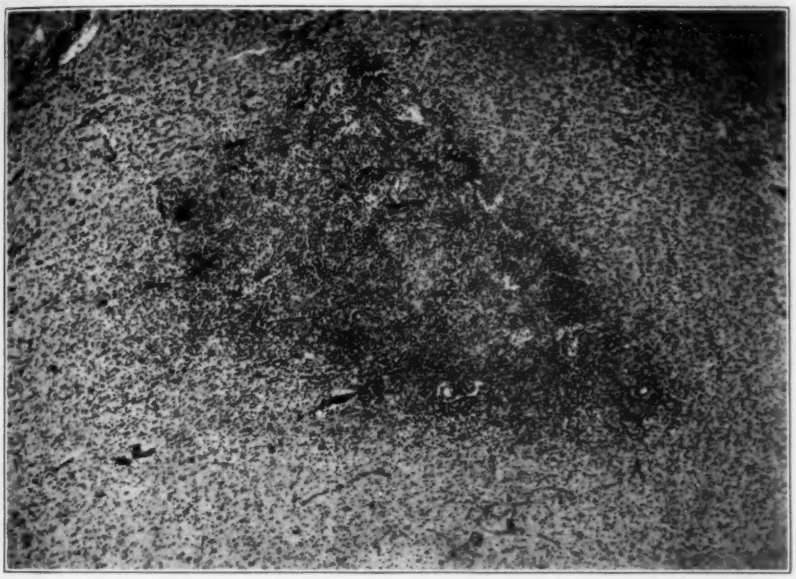

Fig. 7.—Neuroptic myelitis. Focus of degenerative softening in the right optic tract. Toluidine blue stain; × 446.

should indicate that the left optic tract was also normal, that is, that the lesion of the visual fibers was unilateral, as it was in some cases of Katz[9] and Marinesco and his collaborators.[10]

The pia-arachnoid of the brain and spinal cord was thickened and hyperplastic. It contained large hyperemic blood vessels, numerous lymphocytes,

9. Katz, K.: Ueber das Zusammenvorkommen von Neuritis optica und Myelitis acuta, Arch. f. Ophth. **42**:202, 1896.

10. Marinesco, G.; Draganescu, S.; Sager, O., and Grigoresco, D.: Sur une forme particulière anatomo-clinique d'ophthalmo-neuromyélite (ophthalmoencéphalomyélite): Considérations sur les relations avec la maladie de Schilder, la sclérose en plaques et les encéphalo-myélites diffuse postinfectieuses, Rev. neurol. **2**: 193 (Aug.) 1930.

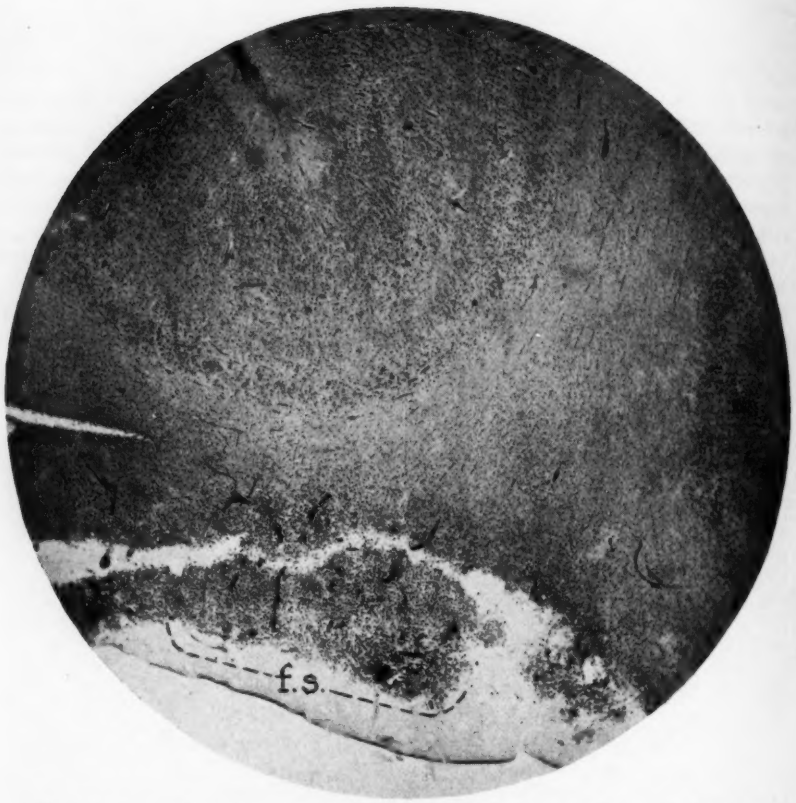

Fig. 8.—A section from the cuneus (right occipital lobe); *f.s.* indicates a focus of softening.

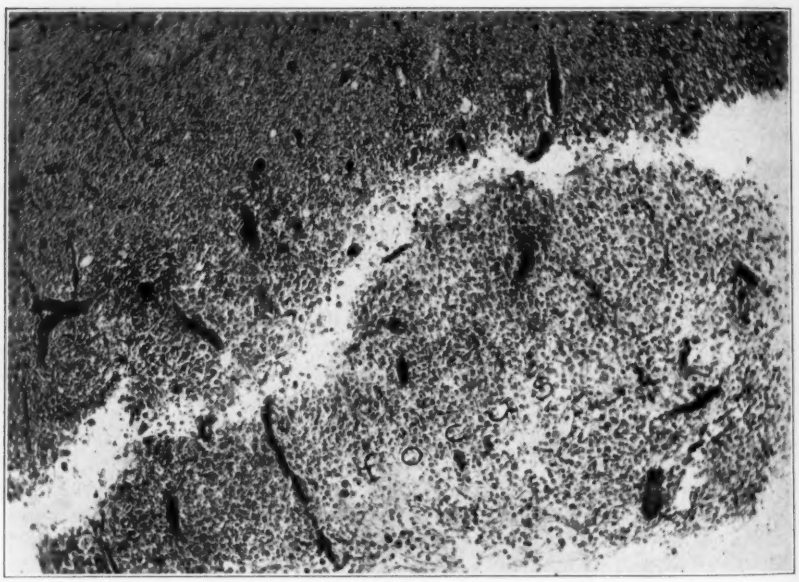

Fig. 9.—Higher magnification of the focus (*f.s.* in figure 8).

degenerated plasma cells, represented by remnants of metachromatically stained cytoplasm and nuclei practically devoid of chromatin, fibroblasts, mast cells and gitter cells. There were no polyblasts or polymorphonuclear cells. Among the cells were scattered nuclei in a state of karyorrhexis. The nuclear contents were broken up into granules that were densely stained, and often only a few such granules remained, lining or even replacing the membrane of the nucleus.

Changes were occasionally present also in the spinal epidural spaces. Vast accumulations of broken-up hematogenous elements, especially in the cervicodorsal region, were present and formed poorly stainable diffuse or nodular cheesy masses which invaded mainly the epidural fat and occasionally the dura itself. These infiltrating epidural masses were probably the cause of the severe pain in the extremities, though no changes were seen in the nerve fibers bridging the space (in the specimens studied) or in the peroneal nerves, the only peripheral nerves examined.

Summary of Histopathologic Observations.—There were: extensive degeneration and invasion of the white and gray substances of the spinal cord, the right optic tract, the right cuneus (especially the subcortical white substance) and a microscopic portion of the internal capsule by microglia and glia cells; occasional breaking up of the fibrillary glia, with formation of filling bodies; occasional infiltration of the blood vessels of the meninges with lymphocytes and gitter cells; infiltration of the epidural space by a necrotic mass, especially in the cervicodorsal region.

COMMENT

The outstanding features in this case (paraplegia, visual disturbances and a short remission) are also observed in multiple sclerosis, in which, however, hemianopia, swelling of the papillae, severe bladder and sensory disturbances and extensive, rapidly spreading trophic disturbances are uncommon. Such signs suggest an acute inflammatory disseminated lesion of the cerebrospinal system. A clinical differential diagnosis between multiple sclerosis and neuroptic myelitis is sometimes difficult, as shown, among others, by Marinesco and his co-workers [10] and van Bogaert.[11] Even pathologically, because of the gross appearance of the patches, these two morbid conditions do resemble each other to such an extent that on the basis of macroscopic changes alone the conclusion would be permissible that neuroptic myelitis and multiple sclerosis are one disease process, the former acute, the latter chronic. Such a view, however, is not sustained by the microscopic characteristics of the patches and other considerations. In neuroptic myelitis the patches invade the gray matter with as great constancy and severity as they do the white matter, affecting not only the nerve fibers but also the ganglion cells of the anterior and posterior cornua. It should be emphasized that the changes in the white and gray substances occur in neuroptic myelitis throughout the spinal cord, even in segments without patches. In my

11. van Bogaert, L.: Erreur de diagnostic; neuromyélite optique aiguë; premier stade d'une sclérose en plaque typique, J. de neurol. et de psychiat. **32**:234 (April) 1932.

case, for instance, swelling of the ganglion cells and proliferation of the microglia were present even in the sacral region, which contained no patches and grossly appeared normal. In multiple sclerosis the gray matter may also be invaded by patches and be extremely cellular even when free from them (fig. 10); yet the ganglion cells are, for the most part, spared and entirely normal in areas devoid of patches, in contrast to what is observed in neuroptic myelitis. In multiple sclerosis patches usually consist of fibrillary astrocytes, their fibers forming a glial scar, whereas in neuroptic myelitis the cells making up the patches or situated outside the latter are microglial, mostly in the form of rod cells. They

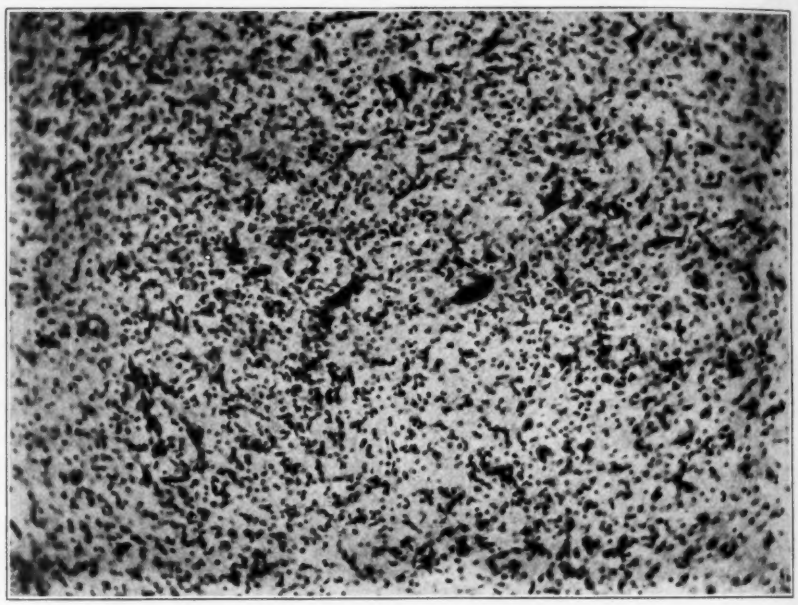

Fig. 10.—Multiple sclerosis. A section showing the cellularity of the anterior horns; the ganglion cells are preserved. The photograph should be contrasted with figure 6, which shows practically similar infiltrations. The magnification and staining are the same as in figure 6.

denote a cellular reaction to a damaged parenchyma and are mixed with cytoplasmic astrocytes, gitter cells, oligodendrocytes and occasionally the "filling bodies" of Alzheimer. The latter were exceptionally numerous in my case, but I have never observed them in multiple sclerosis, in which they evidently do not occur. The gitter cells present in both diseases were not microglial but gliogenous, for it was possible to trace remnants of myelin in their vacuoles, as in any other degeneration of nerve tissues. They may be mixed with lymphocytes, but these are secondary and are always scarce as compared with the masses of gitter

cells. The presence of a few lymphocytes, which are by no means found in every case of multiple sclerosis and are exceedingly rare in typical cases, does not justify a diagnosis of an inflammatory disease process. For if the histologic changes in multiple sclerosis are inflammatory, they should be considered inflammatory also in experimental secondary degeneration—an assumption entirely groundless, for it is not based on facts. Nor are the changes observed in multiple sclerosis and neuroptic myelitis of the type produced by vascular disturbances. In vascular softening of the brain or the spinal cord, both the parenchyma and the glia exhibit massive destruction, being, as it were, cut up by proliferated connective tissue. In multiple sclerosis and neuroptic myelitis, in contrast, the destruction of the nerve tissues is not massive but selective, being replaced not by mesodermal but by glial tissue. In the former it involves the white substance (as in subacute combined degeneration of the spinal cord, Friedreich's ataxia and caisson disease), in which degenerative and normal nerve fibers intermingle, while in neuroptic myelitis it involves the gray substance also. In addition, there is also involvement of the optic nerve fibers (unilateral or bilateral), a combination by no means constant and striking in multiple sclerosis.

An important feature, which I consider specific for multiple sclerosis,[12] is the universal involvement of the white substance of the central nervous system, especially well demonstrable in the spinal cord. The changes in the nerve fibers (swollen myelin, increased number of Elzholz bodies, myeloclasts, etc.) can be revealed also outside the patches, that is, even in areas that are apparently normal, after these have been stained by the methods of Marchi and Bielschowsky or still better when also counterstained by the method of Alzheimer and Mann. Though somewhat altered in structure, such fibers are still capable of performing their function, without exhibiting abnormal clinical signs or symptoms. The changes obviously remain dormant, as it were, just as in a remission during which the patient appears comfortable, though harboring a damaged nervous system. When the clinical features become manifest, appearing even in a mild form, the destruction of nerve tissue has already progressed. That is to say, early as multiple sclerosis may be recognized clinically, pathologically the process is old, having been insidiously progressing for a long time. For instance, it is possible to demonstrate advanced and extensive degenerative nerve lesions in recent multiple sclerosis. In short, in the latter there is no chronological coincidence between the clinical and the pathologic phase, the exact date of the onset of the changes in multiple sclerosis being as indefinite as it is in tabes dorsalis, amyotrophic lateral sclerosis and similar conditions. In neuroptic myelitis such latent widespread lesions in the central nerv-

12. Hassin, George B.: Studies in the Pathology and Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:589 (May) 1922.

ous system do not occur. The short remission in my patient (of three weeks' duration) which followed paralysis of the upper extremity can hardly be considered a proof that her condition was that of multiple sclerosis, since remissions occur also in neuroptic myelitis (Michaux,[2] Beck [13]) as in any other protracted infection or intoxication. Some authors (Beck,[13] Michaux,[2] Cestan, Riser and Planques [14] and Walsch [15]) even think that neuroptic myelitis may end in recovery, basing their views, of course, on clinical observations only. The pathologic features, however, as one can gather from the literature and as presented in this contribution, are of such a nature that recovery cannot be expected. They may be classified, as I have already pointed out, as multiple degenerative softening. It is designated as degenerative because the softening is due not to a vascular disturbance but to direct destruction of the parenchyma by some toxin. The degeneration is acute and affects whole nerve bundles, causing demyelinization, as is well seen, for instance, in peracute postvaccinal or measles encephalitis. In multiple sclerosis such extensive wholesale degeneration of bundles of nerve fibers does not occur, but single nerve fibers undergo successive degeneration, ultimately forming large foci in which various stages of destruction of nerve tissue with or without glial scar formation can be seen. On the basis of the foregoing considerations—the constant combination of visual and spinal cord disturbances, the acute or subacute course of the disease process, the microscopic features of the patches, the type of the glial changes (filling bodies), the simultaneous involvement of the gray and white substances and the condition of apparently normal parts of the nervous system—one is justified in considering neuroptic myelitis a disease process different from multiple sclerosis. For the same reasons, it is not permissible to hold that multiple sclerosis may be a sequel of neuroptic myelitis, as has been maintained by Bouchut and Dechaume [16] and others.

It is customary to designate neuroptic myelitis as acute multiple sclerosis, both clinically and pathologically. As an instance of what is interpreted in the literature as acute multiple sclerosis, I shall cite briefly an exquisite case reported by Guillain and Alajouanine [17] in

13. Beck, G. M.: A Case of Diffuse Myelitis Associated with Optic Neuritis, Brain **50**:687, 1927.

14. Cestan, Riser and Planques: De la neuro-myélite optique, Rev. neurol. **2**:741 (Dec.) 1934.

15. Walsch, Frank B.: Neuromyelitis Optica: An Anatomical Pathological Study of One Case; Clinical Studies of Three Additional Cases, Bull. Johns Hopkins Hosp. **56**:183, 1935.

16. Bouchut, L., and Dechaume, J.: Étude histopathologique d'un cas de neuropticomyélite aiguë, Ann. d'anat. path. **4**:357, 1927.

17. Guillain, George, and Alajouanine, T.: La forme aiguë de la sclérose en plaques, Bull. Acad. de méd., Paris **99**:366, 1928.

which the diagnosis, they emphasized, was based on "facts." The symptoms developed in a patient, aged 35, within fifteen days and lasted three weeks. They were: rigidity of the neck, horizontal nystagmus, normal sensibility, paraplegia, first with a Babinski sign and later flaccid, disturbances of the genito-urinary organs, speech and medulla, with a "subpositive colloidal benzoin" reaction and a negative Wassermann reaction. Microscopic observations (described in thirteen lines) revealed recent patches in the cervical region of the cord, medulla, pons and peduncles. A detailed microscopic description of the patches or other changes was not given. The authors mentioned extensive recent degeneration of the myelin with the formation of myeloclasts, myelophages and nonmobile, fixed gitter cells. No changes were found in the brain proper, and signs of secondary degeneration were also absent. The peracute course of the illness, with the rapid formation of foci of degeneration, in a patient who was suffering from severe toxicity suggests a diagnosis of multiple degenerative softening, a pathologic group with which, as I have pointed out, also belongs neuroptic myelitis.

The exclusively inflammatory features observed in disseminated encephalomyelitis differentiate the latter from both neuroptic myelitis and multiple sclerosis, though theoretically a clinical picture of neuroptic myelitis may be produced by disseminated inflammation of the central nervous system. If such is the case, then neuroptic myelitis should be considered a syndrome caused by either inflammation or degeneration. However, there are no reliable clinicopathologic studies to substantiate the supposition that disseminated encephalomyelitis may cause neuroptic myelitis. Not a single observation of such an occurrence has been quoted by Cournand [18] or Géraud.[19] The case mentioned by Gordon Holmes in the discussion of Beck's[13] paper was most likely one of disseminated encephalomyelitis, though the clinical data cursorily described were too meager to permit a thorough analysis of the case. Good instances are probably the cases of Bouchut and Dechaume [16] and Beck.[13] Bouchut and Dechaume described slight lymphocytic and plasma cell infiltrations of the blood vessels of the meninges and the gray matter of the spinal cord, medulla, pons, peduncles and basal ganglia and partly in the substantia nigra and the cortex of the cerebrum and the cerebellum. Nevertheless, such widespread inflammatory changes denoting disseminated encephalomyelitis were combined with foci of "necrosis" in the spinal cord and nonvascular degenerative changes of

18. Cournand, André: La sclérose en plaques aiguë: Contribution à l'étude des encéphalo-myélites aiguës disséminées, Paris, Amédée Legrand, 1930.

19. Géraud, Jean: De la sclérose en plaques: Etude anatomo-clinique des formes aiguës. Recherches expérimentales. Essai thérapeutique (Sérotherapie "hémolytique"), Paris, J. B. Baillière et fils, 1933.

the white and gray substances (ganglion cells of the ventral horns). In Beck's case also there were pronounced inflammatory and degenerative changes: The demyelinization involved the entire thoracic region of the cord and perivascular cell infiltrations with "round" cells; some plasma and gitter cells were present not only in the cord but also in the brain, cerebellum and meninges. In addition, there were in the lumbar region "areas of exudation," with many polymorphonuclear cells "centered on a vessel." Whatever the significance of the round cells and polymorphonuclear "exudation" was, the inflammatory nature of the pathologic process cannot be doubted. Since the inflammatory changes were recent (polymorphonuclear cells) they cannot explain the vast demyelinization of the spinal cord. As in the case of Bouchut and Dechaume, the demyelinization was the principal histologic feature of a degeneration which, as has been brought out by Barrera,[20] is characteristic of neuroptic myelitis.

For the reasons mentioned, neuroptic myelitis should be considered a definite morbid entity, different from multiple sclerosis and disseminated encephalomyelitis. Its cause is supposed to be a toxic-infectious agent, a neurotropic virus, according to Bouchut and Dechaume.[16] The subacute infectious hyperplasia of the spleen and the suppurative cystitis with bilateral pyelitis in my case may also be considered evidences of a severe infection or toxemia which may produce disseminated changes of the central nervous system designated, as has been pointed out, as multiple or disseminated degenerative softening. This is pathologically altogether different from multiple or disseminated inflammation (encephalomyelitis), but may resemble it clinically. Like disseminated encephalomyelitis, multiple degenerative softening gives rise to a variety of clinical syndromes, some of which possess a fairly definite clinical picture (that of neuroptic myelitis, Schilder's disease and postvaccinal and postmeasles encephalitis). In other forms the clinical picture is less definite. It runs as a protracted and toxic state and may be grouped under the heading of septicemia (Diamond [21]). There is nothing in the aforementioned conditions that would even suggest clinical or histopathologic features of classic multiple sclerosis. Though also a degenerative process, the latter is insidious in onset and progressive in course, and without toxic features, which are so marked in the morbid states grouped by me under the heading of multiple degenerative softening.

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20. Barrera, S. E.: Ophthalmo-Encephalo-Myelopathy: Clinico-Pathological Study of a Case, Psychiatric Quart. **6**:421, 1932.

21. Diamond, I. B.: Changes in the Brain in Pyemia and in Septicemia, Arch. Neurol. & Psychiat. **20**:524 (Sept.) 1928.

CONCLUSIONS

Neuroptic myelitis is a combined patchy degeneration of the spinal cord and the visual fibers.

Macroscopically, the patches resemble those of multiple sclerosis; microscopically, they differ mainly in the scarcity or absence of glia fibers, the simultaneous involvement of the gray and white substances and the massive cellularity.

As in multiple sclerosis, the patches are due to primary degeneration of the nerve fibers.

Excessive cellularity, which is due to an abundance of Hortega cells, is also present but less marked in multiple sclerosis.

Neuroptic myelitis is a definite toxic-infectious disease process, different from multiple sclerosis and disseminated encephalomyelitis.

It may be classified as a form of disseminated softening (degenerative), which constitutes (aside from disseminated tumors) with disseminated inflammation (encephalomyelitis) and disseminated (multiple) sclerosis three separate groups of inflammatory and degenerative diseases differing from one another pathologically and clinically.

SPECIAL ARTICLE

PRIMARY DEMYELINATING PROCESSES OF THE CENTRAL NERVOUS SYSTEM

AN ATTEMPT AT UNIFICATION AND CLASSIFICATION

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NEW YORK

Since Schilder [1] described in 1912 the first case of encephalitis periaxialis diffusa, considerable attention has been paid by investigators to demyelinating processes leading to either patchy or diffuse sclerosis. Numerous cases have been described under the most varied headings: Schilder's disease, encephalitis periaxialis diffusa, symmetrical cerebral central lobar sclerosis (Marie and Foix [2]), encephalopathia scleroticans (Flatau [3]), encephalomyelomalacia chronica diffusa (Hermel [4]), progressive degenerative subcortical encephalopathy (Globus and Strauss [5]), leuko-encephalopathia diffusa (Austregesilo, Gallotti and Borges [6]), sclerotic inflammation of the white matter of the hemispheres (Spielmeyer [7]), leuko-encephalopathia myeloclastica primitiva (Patrassi [8]), encephalopathia extracorticalis diffusa, "Schilder's type" (d'Antona [9]),

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Read in abstract at the Sixty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 2, 1936.

1. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912.

2. Marie, P., and Foix, C.: Sclérose intracérébral centrolobare et symétrique, Rev. neurol. **1**:1, 1914.

3. Flatau, E.: Encephaloleucopathia scleroticans progressiva, Encéphale **20**: 475, 1925.

4. Hermel, H.: Ueber einen Fall von Encephalomyelomalacia chronica diffusa bei einem vierjährigen Kinde, Deutsche Ztschr. f. Nervenh. **68**:335, 1921.

5. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy (Schilder's Disease), Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

6. Austregesilo, M.; Gallotti, O., and Borges, A.: Leucoencéphalopathie diffuse (maladie de Schilder), Rev. neurol. **1**:1, 1930.

7. Spielmeyer, W.: Ueber einige anatomische Aehnlichkeiten zwischen progressiver Paralyse und multipler Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **1**:660, 1910; Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

8. Patrassi, G.: Diffuse Gehirnentmarkungen und sogenannte Encephalitis periaxialis diffusa (Schilder), Virchows Arch. f. path. Anat. **281**:98, 1931.

9. d'Antona, S.: La encephalitis periaxialis diffusa di Schilder (Encephalpathia extracorticalis diffusa, tipo Schilder), Riv. di pat. nerv. **32**:461, 1927.

diffuse sclerosis with preserved myelin islands (Löwenberg and Hill [10]) and encephalitis periaxialis concentrica (Baló [11]).

To these cases must be added those of the familial type described under various headings: by Krabbe,[12] as a new familial infantile form of diffuse cerebral sclerosis occurring in childhood; by Scholz,[13] as familial diffuse brain sclerosis occurring in childhood; by Ferraro,[14] as a familial form of encephalitis periaxialis diffusa; by van Bogaert and Nyssen,[15] as familial progressive leukodystrophy; by Bielschowsky and Henneberg,[16] as leukodystrophia cerebri progressiva hereditaria, and by Pelizaeus [17] and Merzbacher,[18] as aplasia axialis extracorticalis congenita.

In the presence of such an intricate and varied nomenclature, the first question which arises is that concerning the fundamental symptoms and the histopathologic changes common to these various conditions.

From the study of four cases of diffuse sclerosis occurring in my personal experience and from a survey of the literature, I believe that the fundamental histopathologic changes are substantially the same in all the cases reported, irrespective of the name under which they have appeared, and that the clinical manifestations, also fundamentally identical, vary from case to case in relation to the age at onset of the disease, the localization of the process, the intensity of the causative factor, the constitutional make-up of the patient and the particular state of the resistance at the moment of invasion by the pathogenic agent. This explains why d'Antona's [9] contention that a diagnosis of

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10. Löwenberg, K., and Hill, T. S.: Diffuse Sclerosis with Preserved Myelin Islands, Arch. Neurol. & Psychiat. **29**:1232 (June) 1933.

11. Baló, J.: Encephalitis Periaxialis Concentrica, Arch. Neurol. & Psychiat. **19**:242 (Feb.) 1928.

12. Krabbe, K.: Beitrag zur Kenntnis des Frühstadien der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **20**:108, 1913.

13. Scholz, W.: Klinische, pathologisch-anatomische und erbbiologische Untersuchungen bei familiärer, diffuser Hirnsklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:651, 1925.

14. Ferraro, A.: Familiar Form of Encephalitis Periaxialis Diffusa, J. Nerv. & Ment. Dis. **66**:329, 1927.

15. van Bogaert, L., and Nyssen, R.: Le type tardif de la leucodystrophie progressive familiale, Rev. neurol. **65**:21 (Jan.) 1936.

16. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffuse Sklerose (Leukodystrophia cerebri progressiva hereditaria), J. f. Psychol. u. Neurol. **36**: 131, 1928.

17. Pelizaeus, F.: Ueber eine eigenthümliche Form spastischer Lähmung mit Cerebralerscheinungen auf hereditärer Grundlage (multiple Sklerose), Arch. f. Psychiat. **16**:698, 1885.

18. Merzbacher, L.: Eine eigtenartige familiär hereditäre Erkrankungsform (Aplasia axialis extra-corticalis congenital), Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1, 1910.

encephalitis periaxialis diffusa, justified in the presence of a subacute condition in young persons with progressive course, without or with slight fever, with a regular course of mental symptoms and neurologic signs of bilateral character, with symptoms pointing to occipital localization of the process and with motor paralysis ascending from the legs to the arms, applies necessarily to only a limited number of cases. This explains also the correctness of Bouman's [19] contention that it is impossible as yet to discover an approximate unity in the diversity of symptoms in the course of diffuse sclerosis. Neither statement by Collier and Greenfield,[20] that encephalitis periaxialis diffusa is a malady occurring in children and young subjects or that its duration varies from a few months to three years, is likely to cover all the incidences based on age and duration. The incidence varies from case to case, the age of onset ranging from the first months of life to the fifth or the sixth decade and the duration of the disease from a few weeks to twenty and more years. To substantiate these statements, I shall first summarize briefly the clinicopathologic features of the original case described by Schilder.

ENCEPHALITIS PERIAXIALIS DIFFUSA

After a review of Heubner's [21] description of cases of diffuse sclerosis, to which, however, no pathologic report was attached, the cases in which the diagnosis was doubtful, reported by Schmaus,[22] Strümpell,[23] Mingazzini,[24] Weiss [25] and others, and those in which the diagnosis was accepted, reported by Rossolimo,[26] Ceni,[27] Haberfeld and Spieler [28] and

19. Bouman, L.: Diffuse Sclerosis: Encephalitis Periaxialis Diffusa, Bristol, England, John Wright & Sons, Ltd., 1934.

20. Collier, J., and Greenfield, J. E.: The Encephalitis Periaxialis of Schilder (a Clinical and Pathological Study), Brain **47**:489, 1924.

21. Heubner, O.: Ueber diffuse Kirnsklerose, Charité-Ann. **22**:298, 1897.

22. Schmaus, H.: Zur Kenntnis der diffusen Hirnsklerose, Virchows Arch. f. path. Anat. **114**:154, 1888.

23. Strümpell, A.: Ueber diffuse Hirnsklerose, Arch. f. Psychiat. **9**:268, 1879.

24. Mingazzini, G.: Klinische und pathologisch-anatomische Beiträge zur Diagnose und Therapie der Gehirngeschwülste, Deutsche Ztschr. f. Nervenh. **19**:1, 1901.

25. Weiss, G.: Ueber diffuse Sklerose des Hirns und Rückenmarks, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **7**:245, 1900.

26. Rossolimo, G.: Zur Frage über die multiple Sklerose und Gliose, Deutsche Ztschr. f. Nervenh. **11**:88, 1897.

27. Ceni, C.: Ueber einen interessanten Fall gliomatöser Infiltration beider Grosshirnhemisphären, Arch. f. Psychiat. **31**:809, 1899.

28. Haberfeld, W., and Spieler, F.: Zur diffusen Hirn-Rückenmarksklerose im Kindesalter, Deutsche Ztschr. f. Nervenh. **40**:436, 1910.

Beneke,[29] Schilder described the clinical and pathologic details of his case for which he proposed the name "encephalitis periaxialis diffusa."

To compare the observations in Schilder's case with those described subsequently, I report a summary of the clinical findings described by Bouman,[19] who based his study on all the cases of diffuse sclerosis available in the literature up to 1934. Bouman divided the clinical aspects of the disease into those for adolescents and adults and those for children.

CLINICAL OBSERVATIONS

Symptoms in Adults.—In adults the initial symptoms consist generally of disorder of vision and acute blindness and occasionally hemianopia, paresthesias, sevère ataxia and sensory disturbances of objective and subjective types. Now and then pseudobulbar symptoms occur, with a bulbar type of speech and forced crying. Apoplectiform attacks, and in one case epileptiform seizures, were reported. Hemicerebellar symptoms have also occasionally been described as initial symptoms. Unilaterality of symptoms in the course of the disease is more common in adolescents and adults than in children. Disorders of gait (uncertainty, tottering and ataxia) and epileptiform attacks are less frequent in adults than in children. Mental symptoms are frequent and consist generally of forgetfulness, dulness, irritability, disorientation, confusion, euphoria and change of personality and occasionally dementia.

In the fully developed condition acute blindness may appear, associated with optic neuritis and choked disks and partial or total atrophy of the optic nerve. In some cases the fundi are normal. To and fro swinging movements of the eyes have been reported, and external ophthalmoplegia due to involvement of the third nerve is frequent. Involvement of the sixth nerve has been reported. Nystagmus is not common. Paresis of conjugate lateral gaze and hemispasm of the eyelids have been described. The pupils may react sluggishly to light; at times the reaction to light is abolished. Anisocoria is frequent. Absence of the corneal reflexes and analgesia in the territory of the trigeminal nerve have also been found. Disturbance of smell has occasionally been reported. Bulbar symptoms, such as difficulty in swallowing, have also been described. Scanning or slow speech has been mentioned in some cases.

The motor symptoms consist at times of slight paresis of one side, monoplegia, hemiplegia, facial paresis, disturbances in gait and a feeling of heaviness in one arm. The motor symptoms may spread to the opposite side and increase in intensity. Quadriplegia or triplegia is not as frequent in adults and adolescents as in children, though occasionally

29. Beneke: Ein Fall hochgradigster und ausgedehnter diffuser Sklerose des Zentralnervensystems, Arch. f. Kinderh. **47**:420, 1908.

extension contracture of the leg and flexion contracture of the arms have been reported in adults. Rigidity due to involvement of the pyramidal tract is more severe in children. Sometimes flaccid paralysis is noted. Involuntary movements, such as hemiballismus, athetoid movements and grasping and groping movements, may occur. Deep reflexes of medullary automatism and abdominal reflexes are generally absent. Plantar response in extension is not frequent in adults. The reflexes have a certain amount of variability. Apraxia, isolated or associated with alexia or optic agnosia, has been reported.

Muscular atrophy has occasionally been mentioned. Fine tremor of the arm, hand or tongue is more frequent than intention tremor. Symptoms of cerebellar involvement have been reported under the heading of asynergia and adiadokokinesis.

General Symptoms: Stiffness of the neck and symptoms of meningeal irritation have been described. Headaches and vomiting have been mentioned frequently. Less common is vertigo. A rise in temperature has been registered at the onset of the condition or during its course. Depression, visual and auditory hallucinations and a mental picture suggesting schizophrenia occur occasionally.

Cerebrospinal Fluid: Increase in pressure has been mentioned in a few cases. Increase in the amount of globulins and proteins has been reported. The cellular content of the fluid is at times increased.

Remissions have been reported frequently.

The duration of the disease is from a few months to several years.

Symptoms in Children.—Disorder of vision as the initial symptom has been noted in 12 per cent of cases and a combination of disorder of vision and of hearing in 6 per cent. General symptoms, such as headache, vomiting and vertigo, are more common in children than in adults. Convulsions at the onset have been reported. Hemiplegias are less frequent in children; monoplegias are as frequent in children as in adults. Sensory disturbances, such as paresthesia and pains, are not frequent in children. Mental symptoms, such as apathy, irritability, restlessness and change of character, have been observed in about 30 per cent of the cases. Progressive mental deterioration associated with severe cachexia has been reported.

Motor symptoms at the peak of the disease may be represented by paraplegia, triplegia or quadriplegia. Often they are of spastic type, with extension contractures. Pes equinovarus is not rare, with contractures of the adductor muscles. The arms may be extremely flexed at the elbow and the joints of the hands, the arms being closely pressed against the chest and the fingers firmly bent into a fist. Now and then alternating hypertonus and hypotonus occur, probably in connection with the Magnus-Kleyn reflexes. Tonic twitches of the head and neck

and deviation of the head and eyes to one side may be present. In the majority of cases the reflexes are exaggerated. Pathologic reflexes may occur on both sides. The abdominal reflexes are absent in some cases. Ataxia with intention tremor of the arm is not rare; involuntary movements, such as athetoid and choreiform movements, and more frequent.

Reliable data as to sensory changes are mostly lacking; sometimes disorder in the perception of touch has been mentioned. Disorders of smell have been mentioned by a few authors.

Bilateral optic neuritis and particularly atrophy of the optic nerves have often been noted. In some cases temporal pallor has been mentioned. Choked disk is exceptional. In 32 per cent of the cases the fundi were normal. Cerebral blindness, as well as hemianopia, has been noted, but only rarely. The pupillary reactions in many cases are normal; in others they are sluggish or absent. Anisocoria is common, with predominance of mydriasis. In some cases involvement of the sixth nerve is present. Now and then, unilateral ptosis and nystagmus are observed.

In some cases facial paralysis has been mentioned, and now and then deafness precedes or accompanies blindness.

Slow and lalling speech have been frequently reported. Now and then motor or sensory aphasia is present. Most often the disorder of speech is of an articulatory character.

Disturbances in swallowing are particularly frequent—in 38 per cent of the cases. Crying and screaming occur in many instances. There may also be fits of convulsive crying, in which some rhythm may be observed (rhythmic chewing and sucking). During screaming, the spastic phenomena and jerking movements are increased in intensity.

Mentally, forgetfulness, difficulty in thinking and in comprehending, irritability and restlessness accompany the clinical manifestations.

A rise of temperature is noted in some cases. In the infantile familial type a pathologic rise of temperature without demonstrable cause outside the central nervous system has been mentioned.

The protein, globulin and cell contents of the cerebrospinal fluid have been increased in a few cases. Occasionally the colloidal gold curve has been 5555543210 and the benzoin reaction positive.

Comment.—Bouman's summary, which dealt with both the sporadic and the familial cases of diffuse sclerosis, made it evident that in a sufficient number of cases no grouping of symptoms has been reported which is sufficiently consistent to justify the creating of any particular type of diffuse sclerosis.

The opinion of van Bogaert and Nyssen [15] that in the familial form of diffuse sclerosis the infantile type is characterized by predominance

of decerebrate rigidity and epilepsy, the juvenile type by prevalence of choreocerebellar manifestations, with rigidity and athetosis, and the adult type by predominance of akinetic and hyperspasmodic symptoms does not seem to be substantiated by a close scrutiny of the literature.

As the symptomatology and clinical course do not allow the creation of definite clinical types of the disease, can one rely for this on the pathologic changes? Here, also, I shall borrow from Bouman's review the main features of the pathologic process, which are in accord with my personal observations.

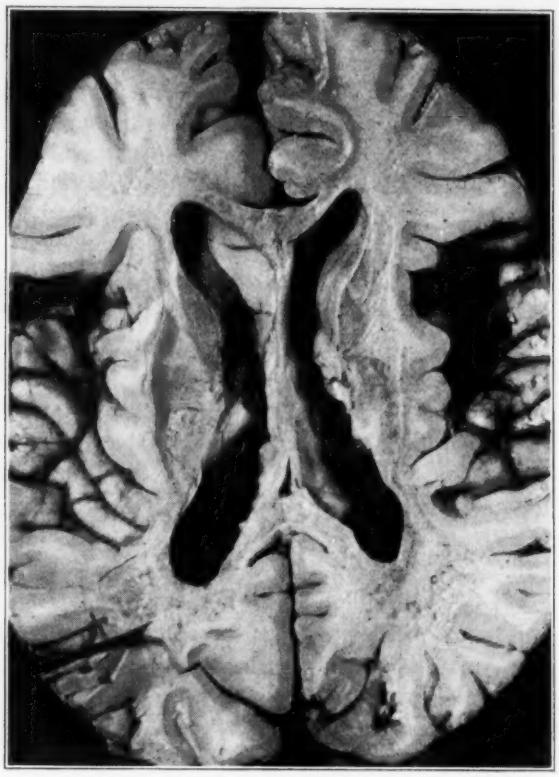

Fig. 1.—Horizontal section of the brain in a case of diffuse sclerosis, showing the characteristic shrunken aspects of the white matter.

PATHOLOGIC CHANGES

Distribution of Lesions.—The demyelinization, which constitutes the fundamental pathologic change of diffuse sclerosis, has no particular location, extending at times from the frontal to the occipital pole in more or less symmetrical fashion. Macroscopically, the sclerotic areas may be recognized by the naked eye (fig. 1). At other times the process predominates in one hemisphere or in one or more lobes. Cases in which

there was predominance of the process in the frontal lobe have been reported, as contrasted with others in which there was predominance in the occipital lobe.

The U fibers have been described frequently as spared by the process of demyelinization, though in many cases they are definitely involved, the demyelinization spreading also into the gray matter.

The patches of demyelinization are generally of large extent, at times invading the whole frontal cross-section of the hemispheres. In many cases the process is limited to the brain, the spinal cord showing only secondary degenerations. In other cases, however, primary patches of demyelinization have also been reported in the brain stem and the spinal cord.

The fundamental histopathologic process in diffuse sclerosis being represented by involvement of the myelin sheaths, these structures may be entirely or partially destroyed. Remnants of myelin may be observed in the center of large patches. Some myelin sheaths may be seen crossing most of the field and presenting a swollen appearance resembling that of a rosary of beads. The demyelinization is marked in the subventricular region. Small patches of demyelinization may be seen fusing together, thus forming larger areas.

Axis-Cylinders.—There is no definite rule concerning the axis-cylinders, their status depending on the intensity of the process. In certain cases they have been reported as severely involved by the lesion, with only remnants to be seen in the demyelinated areas (fig. 2). In other cases axis-cylinders are present in a limited number, some being swollen and tortuous. In less severely involved areas the axis-cylinders may be preserved in considerable number. In the initial phase of the lesions the axis-cylinders may be present, whereas at later stages they are destroyed with the myelin sheaths. Though the destruction of axis-cylinders is primary, secondary degenerations have been reported, particularly in the spinal cord. The demyelinization and destruction of axis-cylinders may occasionally assume a necrotic aspect.

Glial Reaction.—The glial reaction in the center of the patch varies according to the age of the plaque. In the early stages there are numerous globoid cells, *gemästete* glia cells, scattered in the areas of demyelinization, free or surrounded by neuroglia fibrils. As the plaques become old an astrocytic reaction becomes more pronounced, fibrillary astrocytes making their appearance and participating in the process of repair. At the periphery of a plaque considerable hyperplasia and hypertrophy of glial elements take place, which gradually invade the demyelinated area. At a later stage the dense network of glia fibers fills the demyelinated area, a glial scar resulting (fig. 3). Mesodermal

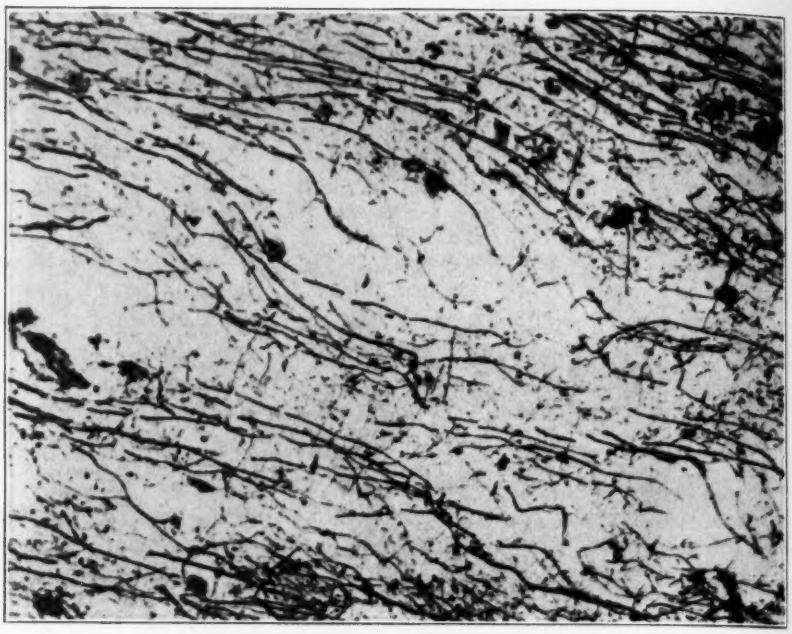

Fig. 2.—Involvement of the axis-cylinders, corresponding to an area of demyelinization, with fragmentation and disappearance of numerous axis-cylinders. Bielschowsky method for neurofibrils.

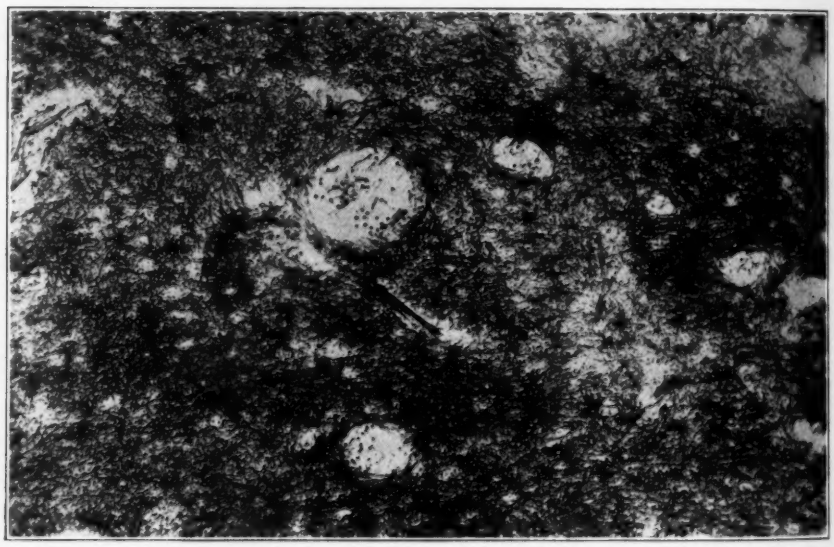

Fig. 3.—Details of the neuroglial reaction in a case of diffuse sclerosis, showing the dense network of glia fibrils replacing myelin sheaths and axis-cylinders. Holzer method for glia fibrils.

elements participate in the scar formation in necrotic areas where the borders between the ectodermal and the mesodermal tissue have been broken down.

Scavenger Cells.—While repair is taking place, the process of clearing away the disintegrated material is carried on by scavenger elements, which are numerous in the foci of demyelinization, especially in those with a slight necrotic tendency. The scavenger cells occur free in the tissue, partaking in the so-called process of *Abbau*. Occasionally oligodendroglia cells and, more frequently, microglial elements are seen becoming transformed into compound granular corpuscles. The fat products of disintegration contained in the scavenger cells, particularly in familial cases (Scholz,[13] Ferraro [14] and Bielschowsky and Henneberg [16]), are not of the brilliant red type seen in the common destructive processes of nerve tissue.

Mucin has been observed in some oligodendroglia cells, in a state of acute swelling (Bailey and Schaltenbrand [30]). Iron pigment occurs in cellular elements surrounding the blood vessels, but its presence has no characteristic significance.

Blood Vessels.—Occasionally there is swelling of the intima, and at times hypertrophy of the adventitia. Lymphocytes and plasma cells surrounding the blood vessels have been reported in several cases, whereas in others no elements of infiltration of this nature have been described. In some instances a mixture of lymphocytes and gitter cells has been described; finally, in others only scavenger cells surrounding the blood vessels have been reported (fig. 4).

Progressive and regressive changes in the walls of the blood vessels have often been reported (proliferation of the elements of the adventitia, with or without hyaline degeneration). The mesenchymal reaction is more pronounced in areas with necrotic tendencies or in small softenings.

Hemorrhages are not constant, though in some instances minute hemorrhages have been detected, some of them having been considered as agonal.

Areas of softening have been encountered in a few cases, and in such instances the process of repair follows the rule of ectodermal and mesodermal collaboration.

As it appears from the preceding pathologic survey of the most important changes in diffuse sclerosis, the histologic observations fail to furnish characteristics of the lesions suitable for differentiating any particular grouping.

30. Bailey, P., and Schaltenbrand, G.: Die muköse Degeneration der Oligodendroglia, Deutsche Ztschr. f. Nervenh. **97**:231, 1927.

It follows that one finds hardly sufficient justification for the use of different names when describing the same fundamental clinicopathologic condition. The name diffuse sclerosis, for instance, carries with it too much implication of a sclerotic stage of glial reaction. The term Schilder's disease does not bring clarification. "Encephalitis periaxialis diffusa" does not provide for cases in which involvement of the axis-cylinders is an important feature. "Central lobar sclerosis" implies too limited a topographic designation of the disease. "Progressive degenerative subcortical encephalopathy" does not sufficiently indicate the

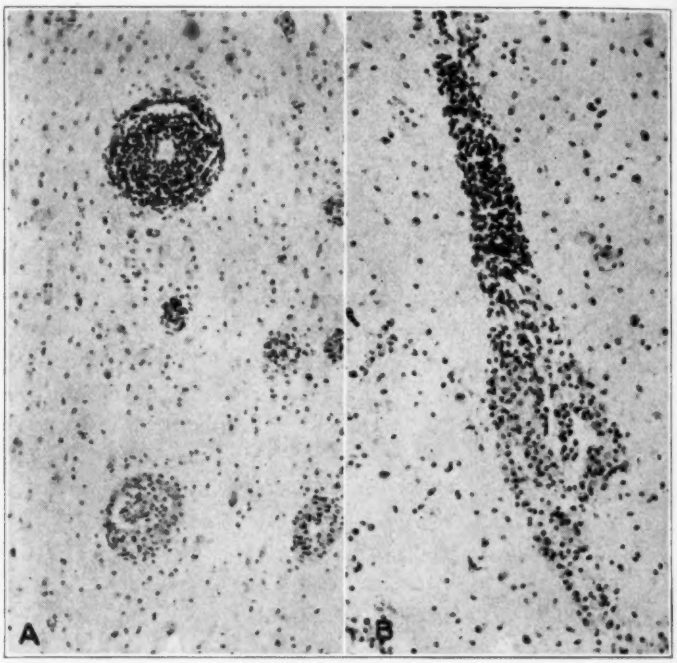

Fig. 4.—Details of the perivascular reaction in a case of diffuse sclerosis. (*A*) A blood vessel in the upper portion of the figure is surrounded by numerous lymphocytes, whereas in the lower portion the blood vessels are surrounded by compound granular corpuscles. (*B*) The upper portion of the blood vessel is surrounded by lymphocytes, whereas the lower portion of the same vessel is surrounded by compound granular corpuscles. Nissl stain.

fundamental condition of demyelinization in the brain and spinal cord, and "leukodystrophy" has the disadvantage of focusing attention on the white matter to the exclusion of the gray matter.

In order to simplify matters, I think that in all clinical cases of the nature under discussion, in which the fundamental pathologic process is suspected to be diffuse demyelinization, it would be better to speak

of a "primary diffuse demyelinating process," which in turn may be qualified according to the course into acute and subacute types.

I advocate, furthermore, a distinction between sporadic and familial cases by labeling the diffuse demyelinating process according to its familial or its sporadic character.

This simplified terminology has the advantage of not binding one to the factors of the extent or intensity of the process, which vary from case to case, or to the different types of tissue reaction, which depend on the pathways of spread of the pathogenic agent, or on the age and constitution of the patient affected.

Before entering, however, into a more detailed discussion of the classification and nomenclature of the demyelinating processes proposed, I think it necessary first to analyze the right to autonomy that some demyelinating processes have been accorded through the tendency to label a disease by the name of the author who first concerned himself in detail with its study, a tendency which has resulted in the creation of artificial nosologic entities, elimination of which will, in my estimation, clarify the situation.

I refer here to both the sporadic and the familial groups of diffuse sclerosis, from which at least three clinicopathologic entities have been created: (1) from the group of sporadic cases, Baló's disease, and (2) from the group of familial cases, (*a*) Krabbe's disease and (*b*) Pelizaeus-Merzbacher's disease.

In the following summary of the clinical and pathologic features of each of these conditions, I have attempted to show the considerable analogies of both the clinical and the pathologic manifestations, which, on closer study, greatly weaken their right to an autonomy that has been accepted by many clinicians.

SPORADIC CASES

Baló's Disease.—Marburg [31] described a case, his third, in which histologic study disclosed the existence of a particular type of demyelinization consisting of an irregular appearance and a tendency to concentric distribution of the demyelinated layers, so as to reproduce the aspect of a geographic map.

The case was that of a woman aged 30 in whom in fifteen days a syndrome of cerebral hypertension and mental disturbances gradually became established. She complained also of vomiting and severe headache, became rapidly apathetic and somnolent and laughed without motivation. She was disoriented and presented hiccups and incontinence of urine. She could not stand and had a tendency to fall backward, while deviating toward the left. The achilles reflex

31. Marburg, O.: Die sogenannte „akute multiple Sklerose" (Encephalomyelitis periaxialis scleroticans), Jahrb. f. Psychiat. u. Neurol. **27**:213, 1906.

was more lively on the right. On the following day she slept and answered only rarely to questions. The left leg was paretic. The paresis rapidly increased in intensity, and a Babinski sign appeared. Somnolence became more marked. Respiration was of the Cheyne-Stokes type. Feeding became impossible. Incontinence of feces appeared. The patient died twelve days after her admission to the clinic.

Histologically, the characteristic type of demyelinization already mentioned was observed in the white matter of the right hemisphere. In the left hemisphere the same type of lesion was present but was less pronounced. Moreover, patches of demyelinization typical of multiple sclerosis were observed in the brain. The brain stem, the cerebellum and the spinal cord were intact.

Baló [11] reported a case of so-called encephalitis periaxialis diffusa.

A man aged 23 presented first agraphia and then aphasia. These disturbances developed in the course of one month and were followed by the rapid appearance of paresis of the right side of the face. The movements of the hands became clumsy. The first neurologic examination revealed facial paresis, absence of pharyngeal reflexes, a certain amount of dysmetria and inability to write words or letters which he knew. There was absence of the abdominal reflexes on the right. The movements of the right hand were slightly impaired. Two months later right hemiplegia was present and was accompanied by headache, nausea and vomiting. Speech was more disturbed, and there were incontinence of urine and tonic spasms in the extremities involved. Cremasteric reflexes were abolished on both sides, and abdominal reflexes on the right. The tendon reflexes in both lower extremities and in the upper right extremity were pronounced. There were ankle clonus, a Babinski sign and facial paralysis of central origin on the right.

In addition, there was bilateral optic neuritis, with edematous disks. The blood vessels were not particularly dilated. The retina in the vicinity of the disk was also edematous. Sensory aphasia was total. The right upper extremity was hypertonic, as were the muscles of the neck on the same side. Lumbar puncture disclosed hypertension of the fluid, but no cellular variation. The clinical diagnosis was tumor in Broca's area. Operation was performed. The patient died on the day after operation.

The interesting pathologic feature in this case is the presence of diffuse demyelinization, which at the level of the anterior horn of the lateral ventricle, presented a well defined concentric aspect visible to the naked eye. Macroscopically, the concentric focus in the right hemisphere consisted of alternating gray and white layers. The center of the focus was an elliptic area, 3 by 1.5 mm. (fig. 5). Around this concentric rings, composed of alternating gray and white lamellae, were present. Near the center the rings were about 1 mm. thick, while the peripheral rings were wider. It is of interest that where the focus approached the cortex the rings were interrupted. In the white matter of the left hemisphere there were scattered spotted gray dots, the size of a millet seed or of lentils, often fusing together. In the white substance of the inferior frontal gyrus, adjacent to the gray matter, concentric stripes ran parallel to the surface. In some areas irregular spots were present, but no concentric rings had developed. The striatum and the internal capsule appeared normal. Dots and concentric layers were present throughout the white matter of the hemispheres, but were not as pronounced as in the most frontal portion. The pons, medulla and spinal cord did not present pathologic lesions. Histologically, in the concentric areas, there was destruction of the myelin sheaths and axis-cylinders. A neuroglial reaction was considerably greater

in the center than at the periphery of the foci, suggesting that the degeneration of the medullary sheaths began at the center. In some parts of the brain, in which there were no concentric foci but only smaller gray areas, degeneration of the medullary sheaths with intact axis-cylinders was associated with a reactive proliferation of neuroglia. The blood vessels in the areas of demyelinization showed perivascular infiltration consisting of compound granular corpuscles, lymphocytes and plasma cells. Large mononucleated cells were also seen. In the brain perivascular infiltration occurred also in the vicinity of the demyelinated areas. The meninges were slightly infiltrated. An interesting type of lesion in the blood vessels was hyaline thickening of the arteries, not only in the foci but in areas far from the foci, in the leptomeninges and the basal ganglia. The hyaline wall of the arteries was sometimes surrounded by perivascular infiltration.

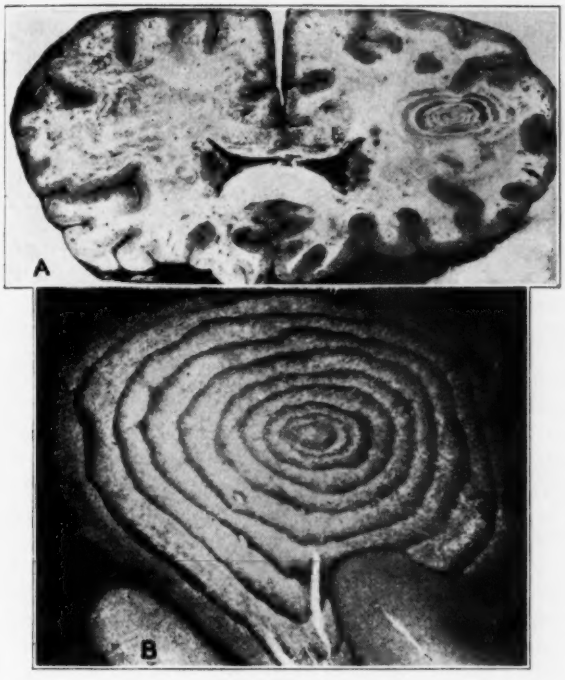

Fig. 5.—Macroscopic aspect of an area of concentric demyelinization, shown (*A*) with low power and (*B*) with high power (after Baló [11]).

Baló expressed the belief that concentric demyelinization was the result of a lecithinolytic action on the myelin sheaths. He was unable to demonstrate any known pathogenic agent or filtrable virus. He had no explanation for the fact that some lines of white matter remained intact while others were destroyed. Local immunity of the tissues might have played a part in this aspect of the phenomenon.

On the basis of the presence of the peculiar concentric aspect of the lesions, Baló expressed the opinion that the condition in his case should

be differentiated from the usual forms of encephalitis periaxialis diffusa and suggested the name "leuko-encephalitis periaxialis concentrica."

Barrè, Morin, Draganesco and Reys [32] published, under the name "Encephalitis periaxialis diffusa," a clinicopathologic report of a case in which the demyelinization had the characteristic concentric appearance described in Marburg's third case of acute multiple sclerosis. It was only after the publication of Baló's work, in 1933, that a revision of the diagnosis was made and a report of the same case was published again by Barré and van Bogaert,[33] under the name "subacute leuko-encephalitis, concentric type of Baló." On the basis of a study of their own case and those of Marburg, Baló and Patrassi, Barré and his co-workers reached the conclusion that in the large group of forms of leuko-encephalitis the concentric subacute type of Baló seems to constitute an autonomic clinicopathologic type.

Hallervorden and Spatz [34] described two new cases of concentric sclerosis.

The first case was that of a patient aged 24 in whom difficulty in writing and paresthesia appeared first, followed by paresis of the right hand. In the course of three or four weeks a motor type of speech defect and difficulty in walking were present. On admission to the psychiatric clinic in the fourth week of the disease, spastic paralysis of the right arm and paresis of the right leg were found. Later, bilateral supranuclear paresis of practically all the motor cranial nerves was established. In the sensory field, only light hypesthesia of the right side of the face and diminution of the right corneal reflex were noticed. The sensory organs were not involved. The fundi presented chronic optic neuritis. Gradually the patient became unable to articulate, while understanding of spoken language was preserved, and orders were carried out with the left hand. The patient died of pneumonia. Examination of the cerebrospinal fluid revealed 142 cells, mostly lymphocytes, and increase in protein; the pressure was 204 mm. of water. The disease lasted five or six weeks. The clinical diagnosis was meningo-encephalitis; tuberculosis was believed to be the causative agent.

The second case was that of a woman aged 51, who was first examined after she had been paralyzed on the right side for several months. During that time there had been hypertonus of the right arm, fingers and legs. The patient was completely demented and aphasic. The right pupil was larger than the left, and reaction to light was impaired. The pressure of the cerebrospinal fluid was 170 mm., and there were 28 cells. One and one-half years later the condition was practically the same. The reflexes on the right could not be elicited; those on the left were present. The rigidity was particularly strong. There were paresis of

32. Barrè, L.; Morin; Draganesco, S., and Reys, L.: Encéphalite périaxiale diffuse (type Schilder), Rev. neurol. **2**:541, 1926.

33. Barré, J. A., and van Bogaert, L.: Contribution à la dissociation anatomique et clinique des leuco-encéphalites subaiguës; Le type concentrique de Baló, Rev. neurol. **1**:547, 1933.

34. Hallervorden, J., and Spatz, H.: Ueber die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprozessen, Arch. f. Psychiat. **98**:641, 1933.

the right side of the face and ptosis of the right eyelid; no nystagmus was noted. The patient was demented and disoriented and spoke unintelligibly. Decubitus set in. Cramplike movements of the right side of the face and painful muscular contraction appeared. Death occurred two years after onset of the disease.

In both cases autopsy revealed diffuse concentric areas of demyelinization, some of which appeared as parallel, alternating rows of myelinated and demyelinated areas. In the second case, in addition to the concentric areas, there was a large area of demyelinization of the type observed in the common form of diffuse sclerosis. Small areas of demyelinization of the type seen in multiple sclerosis were also present as in the case of Marburg. In the first case there was massive infiltration of the meninges with lymphocytes and plasma cells and perivascular infiltration of the blood vessels in the whole brain substance. The right optic nerve showed chronic interstitial neuritis, with slight atrophy of the nasal portion. The perivascular infiltration was not pronounced in the brain stem or the cerebellum. There was no degeneration of the pyramidal tracts. In the second case an inflammatory reaction was observed only in the patches of demyelinization.

It seems to me that neither from the clinical nor from the pathologic standpoint are there sufficient elements to justify consideration of so-called Baló's disease as a clinicopathologic entity. Clinically, the only common feature is the occurrence of right hemiplegia in most cases; in Marburg's case the motor disturbance was on the left. Involvement of the optic system was present in all the cases described but did not differ from the changes reported in cases of the common type of diffuse sclerosis. The age at onset varied from 10 years, in Patrassi's case, to 51, in the second case of Hallervorden and Spatz; this does not establish any particular value for this feature, as was thought by Barré and van Bogaert. The duration of the disease varied from four weeks, in Marburg's case, to from two to three years, in Barré's case.

The onset as hemiplegia in other types of diffuse sclerosis is not rare; Schilder's first case, on which the creation of Schilder's disease depended, was one in which, after involvement of the optic system, right hemiplegia developed. The occurrence of involuntary movement and cramplike manifestations has also been described in cases of the common type of diffuse sclerosis (Guillain, Alajouanine, Bertrand and Garcin [35]). Finally, the forced twist of the head to one side was described in Schilder's first case and in certain cases of familial diffuse sclerosis (Pelizaeus-Merzbacher's type).

From the histologic standpoint, against the clinicopathologic autonomy of the concentric type of diffuse sclerosis I may mention that in cases of typical multiple sclerosis Steiner described the occurrence of special areas in which the demyelinization presented a characteristic concentric distribution. Two such areas were illustrated in his mono-

35. Guillain, G.; Alajouanine, T.; Bertrand, I., and Garcin, R.: Sur une forme anatomo-clinique spéciale de neuromyélite optique nécrotique aiguë avec crises toniques tetanoïdes: Contribution à l'étude des crises toniques sous-corticales, Ann. de méd. **24**:24, 1928.

graph (page 116, figs. 33 and 34).[36] Henneberg,[37] in a patient aged 30, suffering from a subacute type of multiple sclerosis, also described an area of demyelinization in which streaks of myelin sheaths were preserved in the posterior horn of the lateral ventricle. Finally, Hallervorden[38] described concentric demyelinization in a case of typical multiple sclerosis.

In cases of diffuse sclerosis the association of diffuse demyelinization with areas of concentric demyelinization has also been reported. In a case described as one of diffuse sclerosis by Löwenberg,[39] the occurrence of irregular concentric lines of preserved myelin sheaths was reported by Spatz and Hallervorden, who cited also the case of Ostertag, in which a layering of demyelinated lines was present. The same may be said of the cases of Benoit and Caspers.

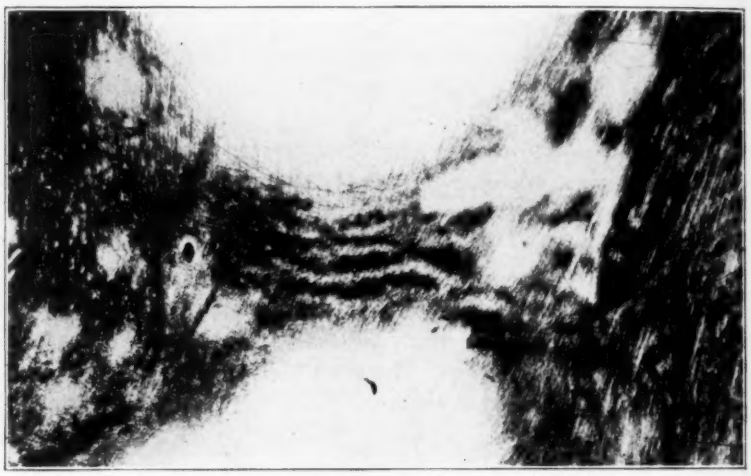

Fig. 6.—Parallel distribution of alternate rows of demyelinization in a case of acute encephalomyelitis, as compared with the same changes in some of the areas shown in figure 5. Spielmeyer method for myelin sheaths.

In a case of acute encephalomyelitis which I described with Jervis,[40] there were in some sections typical areas of concentric demyelinization

36. Steiner, G.: Krankheitserreger und Gewebsbefund bei multipler Sklerose, Berlin, Julius Springer, 1931.

37. Henneberg, R.: Ueber disseminierte Enzephalitis, Neurol. Centralbl. **35:** 652 and 984, 1916.

38. Hallervorden, J.: Eigenartige und nicht rubrizierbare Prozesse, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 305.

39. Löwenberg, K., quoted by Hallervorden and Spatz.[34]

40. Ferraro, A., and Jervis, G.: Acute Demyelinizing Disseminated Encephalomyelitis, New York State J. Med. **36:**139 (Feb. 1) 1936.

(fig. 6). These areas were part of the changes represented by an association of diffuse, concentric and patchy demyelinization, the last resembling the type seen in multiple sclerosis.

Finally, in my experimental work on intoxication with potassium cyanide,[41] I observed in several instances the association of areas of the diffuse and the concentric type of demyelinization (fig. 7).

Hallervorden and Spatz expressed the belief that histopathologically the structure of the isolated foci is identical in the multiple, the diffuse

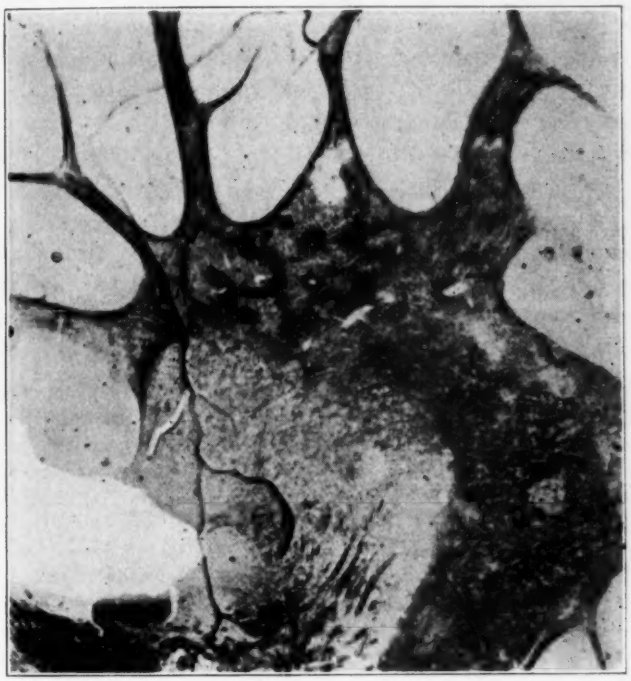

Fig. 7.—Irregularity of the process of demyelinization in experimental cyanide poisoning in a cat, as compared with aspects in the concentric type of demyelinization. Spielmeyer method for myelin sheaths.

and the concentric type of sclerosis. Their impression was that demyelinization in a concentric form is related to the physicochemical type of diffusion of the toxic substance affecting the myelin sheaths. The process is comparable with the colloidal rings known as *Liesegang* rings.

41. Ferraro, A.: Experimental Toxic Encephalomyelopathy (Diffuse Sclerosis Following Subcutaneous Injections of Potassium Cyanide), Psychiatric Quart. **7**:267, 1933.

They agreed with Gozzano and Vizioli [42] in their contention that diffusion of the noxae in diffuse sclerosis may start from the ventricle and invade generally the white substance. This type of diffusion would be in addition to that of a toxin from the blood vessels, which is more likely to occur in multiple sclerosis. The type of diffusion does not, however, give any indication as to the origin of the myelinolytic substance—whether derived from internal metabolism or produced locally by a pathogenic agent.

The number of reported cases of Baló's type is too limited as yet to allow a final opinion as to the nosologic entity, but I believe that the clinical analogies in the cases described and in others of common diffuse sclerosis and the occurrence from the pathologic standpoint of transitional areas of the diffuse, patchy and concentric aspects of demyelinization are elements pointing to lack of a sufficient reason for considering at present Baló's type of demyelinization as the expression of a separate clinicopathologic entity.

FAMILIAL CASES

Krabbe's Disease.—Krabbe,[43] under the heading "a familial infantile form of diffuse brain sclerosis," described five cases of the disease, the first two belonging in the same family, the second two in another family and the last being sporadic.

> Histopathologically, the characteristic features were complete destruction of the medullary sheaths and axis-cylinders, replacement of the destroyed tissue by neuroglia and relative intactness of the nerve cells. Demeylinization, present in all areas of the white matter, also involved the basal ganglia and the spinal cord. Considerable numbers of compound granular corpuscles were free in the patches of demyelinization and around blood vessels. According to Krabbe, this picture corresponds exactly to the initial stage of diffuse sclerosis; the disease is not inflammatory, as leukocytes, lymphocytes or plasma cells were not observed anywhere. "I am compelled, therefore," he continued, "to refer the disease to a more degenerative process." He also asserted that degeneration of the myelin sheaths and axis-cylinders is the primary factor in the disease, whereas the glial proliferation and infiltration of the medullary sheaths with gliogenous fatty granular cells and other scavenger cells represent a secondary process.

Krabbe, having divided the forms of diffuse sclerosis into three groups, (1) the syphilitic type, (2) encephalitis periaxialis diffusa and (3) the familial infantile form of diffuse brain sclerosis, classified his cases in the third group. In this group he included, moreover, a case of diffuse sclerosis described by Beneke [29] in a boy aged 1 year and 9

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42. Gozzano, M., and Vizioli, F.: La encefalopatia periassiale diffusa di Schilder ed i suoi rapporti con la sclerosi a placche contributo clinico e anatomopatologico, Riv. di neurol. **5**:257, 1932.

43. Krabbe, K.: A New Familial Infantile Form of Diffuse Brain-Sclerosis, Brain **39**:74, 1916.

months. The only difference between Beneke's case and Krabbe's cases is that the process was not so advanced in Beneke's case. Krabbe also expressed the belief that the condition in his cases had a certain relationship to Pelizaeus-Merzbacher's disease, as the latter appears during the first year of life and results in pronounced destruction of the white matter of the brain. "But," continued Krabbe, "there is a considerable difference in the clinical picture and in the course of the disease." Of interest is the fact that though not sure of his views, Krabbe tended to classify in the third group of a familial form of diffuse sclerosis the cases reported by Schmaus and Heubner which, in turn, were stated by Schilder to be representative of the group of encephalitis periaxialis diffusa.

Pelizaeus-Merzbacher's Disease.—This condition, first described clinically by Pelizaeus [17] and later histologically by Merzbacher [18] (1910), is merely a variety of diffuse sclerosis with a familial trend, as in the cases described by Pelizaeus it attacked as many as four generations of the same stock. Only a few cases have been reported in the literature.

The disease generally begins in the first months of life, at times at the end of the first year, with nystagmus and tremor of the head and neck. From the onset the progression of symptoms is rapid until the sixth year; they consist of spasticity, particularly of the lower extremities, ataxia, intention tremors, dysarthria, paresis of the muscles of the back, abdomen, hips and legs, pronounced contracture, muscular atrophies, athetoid and choreiform movements, vasomotor disturbances (cyanosis), trophic changes, skeletal deformities (kyphoscoliosis), bradylalia, exaggeration and occasionally absence of deep tendon reflexes, loss of abdominal reflexes and a Babinski sign. Marked tremors were reported by Batten and Wilkinson [44] in their cases in which the disease was suspected. Sensory changes and disturbances of the sphincters were not observed in the early stages, though disturbances of the sphincters were reported by Merzbacher and by Bodechtel.[45] Ticlike movements of the head resulting from traction of the sternocleidomastoid muscles were reported by Bostroem.[46] In the cases reported by Bostroem and Bodechtel nystagmus was not present. In contrast to the condition in the cases of Pelizaeus and others who reported normal eyegrounds, marked temporal pallor of the disks was reported in Bostroem's cases. In some cases the pallor involved three fourths of

44. Batten, F., and Wilkinson, D.: Unusual Type of Hereditary Disease of the Nervous System (Pelizaeus-Merzbacher), Aplasia Axialis Extra-Corticalis Congenita, Brain **36**:341, 1914.

45. Bodechtel, G.: Zur Frage der Pelizaeus-Merzbacherschen Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:487, 1929.

46. Bostroem, A.: Ueber die Pelizaeus-Merzbacher'sche Krankheit, Deutsche Ztschr. f. Nervenh. **100**:63, 1927.

the disk and was correlated by Bostroem with possible retrobulbar neuritis. In some cases no mental changes were reported, whereas in others gradual deterioration progressed with the disease. Bostroem expressed the opinion, however, that intellectually the patient should be evaluated by taking into account the peripheral handicap of poor vision, speech difficulty and marked motor disability.

In the original case of Pelizaeus-Merzbacher's disease, in the case of Liebers [47] and in most of the cases of Bostroem, the disease began during the first year of life. Bodechtel reported, however, onset in his case at the age of 5 years; Löwenberg and Hill [10] placed the onset in their case in the fifth decade of life. In one of the cases of Scheftel in which the disease was suspected,[48] the first neurologic symptoms were discovered when the patient was 17 years old, at which time his intelligence quotient was 95 and his mental age 6 years. Five years later he began to show choreiform movements.

Remissions were reported only in Scheftel's patient.

Histopathologically, the disease is represented by diffuse demyelinization, varying in distribution, invading large areas of the white substance of the brain and generally sparing the U fibers. The sparing of these fibers is not constant, however, Bodechtel having reported invasion of the U fibers in his case.

The demyelinization in Pelizaeus-Merzbacher's disease is not limited to the white substance of the brain but in some cases reported involved the brain stem and the spinal cord (Liebers [47]).

Both macroscopically and microscopically the pathologic observations in Pelizaeus-Merzbacher's disease do not differ from those described in diffuse sclerosis. An attempt has been made to consider the preservation of myelin around some of the blood vessels as characteristic of Pelizaeus-Merzbacher's disease. Thus, Löwenberg and Hill spoke of preserved myelin islands. This preservation, however, is not constant, as Bodechtel mentioned the scarcity of preserved perivascular myelin islands in his case, this constituting from the standpoint of these areas a transition to the condition in diffuse sclerosis. It has also been pointed out that in Pelizaeus-Merzbacher's disease linear areas of preserved myelin are common. This character was not reported, however, in the case of Bodechtel; on the other hand, if present, it does not differ from the incomplete concentric demyelinization observed in some cases of diffuse and acute sclerosis.

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47. Liebers, M.: Zur Histopathologie des zweiten Falles von Pelizaeus-Merzbacherscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **115**:487, 1928.

48. Scheftel, Y.: Pelizaeus-Merzbacher Disease (Familial Centro-Lobar Sclerosis), J. Nerv. & Ment. Dis. **74**:185, 1931.

Therefore, histologically there are no appreciable elements by which one can differentiate between Pelizaeus-Merzbacher's disease and the common type of diffuse sclerosis. Sheftel spoke of Pelizaeus-Merzbacher's disease as a familial centrolobar sclerosis, a term used by Marie and Foix in describing so-called Schilder's disease.

The clinical symptoms in Pelizaeus-Merzbacher's disease are not substantially different from those described in diffuse sclerosis. The onset does not differ from that reported in some of the common forms or from that described in Krabbe's cases; if it is true that the disease lasts a long time—for two or three decades—the duration does not vary from that reported in a number of other common forms of diffuse sclerosis.

Altogether, there does not seem to be sufficient grounds for the creation of a new clinicopathologic entity. Pelizaeus-Merzbacher's disease does not seem to differ from other forms of familial diffuse sclerosis developing in the early months of life. Its only particular feature, represented by the chronic course of the disease, does not constitute, it seems to me, sufficient reason for its autonomy. The classification with the variety of chronic forms of the familial type of demyelinating processes gives, in my opinion, the process enough individuality, without the necessity of resorting to the creation of a new disease.

On the basis of the survey of clinical and histopathologic observations in the conditions already discussed, I believe that in sporadic cases sufficient elements are available to conclude that all are fundamentally the same clinicopathologic entity, with variations from case to case due to the age of the patient and possibly to the intensity of the pathogenic agents in relation to the resistance of the invaded tissue. The familial occurrence of the disease in some cases reported does not constitute sufficient grounds for advocating a new disease. At the most, constitutional factors play here a more important rôle than in the sporadic cases. The occurrence of familial cases of senile psychosis, tuberous sclerosis and dementia praecox, for instance, does not justify the labeling of such diseases as heredodegenerative. Though a distinct grouping of the familial cases is justified, more material must be studied before reaching the conclusion that they are an expression of a fundamentally different disease.

The question which follows concerns the relationship between diffuse sclerosis and multiple sclerosis. From the description of the fundamental pathologic lesions in diffuse sclerosis, it is justifiable to assume that the lesions are not different from those in multiple sclerosis. The clinical course is also at times identical in the two conditions; cases have been reported in which a differential diagnosis between diffuse and multiple sclerosis is difficult to make. It may be added that, as in diffuse sclerosis, familial cases of multiple sclerosis have recently been

described (Laignel-Lavastine and Koressios,[49] Dereux and Pruvost,[50] Ottonello [51] and Curtius [52]).

Analogies and identities between multiple sclerosis and diffuse sclerosis are striking histologically; patches of multiple sclerosis occur near areas of diffuse sclerosis in the brain and in the spinal cord. Bouman pointed out the presence of numerous small, sharply limited demyelinated areas in the brain stem, which were identical with patches of early disseminated sclerosis. Kufs [53] also (in case 1) observed patches of disseminated sclerosis in the left thalamus, the pons, the medulla and the cerebellum and spoke of transitional forms between diffuse and disseminated sclerosis. Similar insular patches, reminiscent of diffuse sclerosis, were described by Gagel [54] in a case of sclerosis following measles. In Schaltenbrand's [55] cases patches of disseminated sclerosis were present in the optic chiasm and the optic tract. In Beneke's case patches of demyelinization strongly resembling those of disseminated sclerosis were present in the spinal cord. Jakob,[56] too, described in the neighborhood of secondary degenerations patches of demyelinization in the pons, the medulla oblongata and the spinal cord in cases of diffuse sclerosis. Wertham [57] observed an association of diffuse sclerosis and patches of multiple sclerosis in the posterior column of the cervical region of the cord, in which fibrous gliosis had replaced the myelin sheaths. In case 2 in his report small patches of demyelinization were present in the cerebellum, the pons, the tegmentum and the medulla

49. Laignel-Lavastine and Koressios, N.: Un cas de sclérose en plaques probablement familiale, Rev. neurol. **64**:914, 1935.

50. Dereux, J., and Pruvost, A.: Sclérose en plaques familiale, Rev. neurol. **65**:351, 1936.

51. Ottonello, P.: Varietà infanto-familiare della malattia di Schilder, Riv. di pat. nerv. **42**:416, 1933.

52. Curtius, F.: Multiple Sklerose und Erbanlage, Leipzig, Georg Thieme, 1933.

53. Kufs, H.: Ein bemerkenswerter Uebergangsfall von diffuser zu multipler Hirnsklerose mit dem Beginn der Krankheit im 63. Lebensjahre und über einem Fall von Heubnerscher Form der diffusen Hirnsklerose, Arch. f. Psychiat. **93**: 564, 1931.

54. Gagel, O.: Zur Frage der diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:418, 1927.

55. Schaltenbrand, G.: Encephalitis Periaxialis Diffusa (Schilder): A Case Report with Clinical and Anatomic Studies, Arch. Neurol. & Psychiat. **18**:944 (Dec.) 1927.

56. Jakob, A.: Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihren Beziehungen zur diffusen und multiplen Sklerosis, Ztschr. f. d. ges. Neurol. u. Psychiat. **27**:290, 1915.

57. Wertham, F.: Small Foci of Demyelinization in the Cortex and Spinal Cord in Diffuse Sclerosis: Their Similarity to Those of Disseminated Sclerosis and Dementia Paralytica, Arch. Neurol. & Psychiat. **27**:1380 (June) 1932.

oblongata. Bielschowsky and Maas [58] mentioned scattered foci with the characteristics typical of polysclerotic plaques in the neighborhood of areas of diffuse demyelinization. In the spinal cord in their case there were also patches of localized sclerosis.

D'Antona [9] described small areas of demyelinization which were independent of the larger patches. In the third case of Neubürger,[59] which he described as one of multiple sclerosis, the histopathologic characters, distribution and extent of the lesions resembled more those of diffuse sclerosis than those of multiple sclerosis (d'Antona). In the case described by Austregesilo, Gallotti and Borges [6] small areas of demyelinization of the white substance of the brain were present in the neighborhood of areas of diffuse sclerosis. In the case described by Urechia, Mihalescu and Elekes [60] small patches of isolated sclerosis were present in the spinal cord, contrasting with the diffuse demyelinization of the brain. In the second of three cases described by Stewart, Greenfield and Blandy [61] there were isolated plaques in the medulla; in the third case there were small areas of demyelinization, not easily to be differentiated from areas of multiple sclerosis, in the optic nerves, the mesencephalon, the pons, the cerebellum and the spinal cord.

Guttmann's [62] case is of particular interest, if considered as one of diffuse sclerosis, because while one hemisphere disclosed the characters of diffuse sclerosis the other showed only small, localized patches of demyelinization.

In a case of diffuse sclerosis characterized clinically by the occurrence of a schizophrenic syndrome, I [63] reported the presence of small areas of sclerosis in the pons, which contrasted with the large, diffuse areas in the brain and cerebellum (fig. 8*A*).

Gozzano and Vizioli described, in a case of periaxial diffuse encephalopathy, small foci in the brain and spinal cord (fig. 8*B*) which could not be differentiated from those of multiple sclerosis; they concluded that all attempts to separate Schilder's disease from multiple sclerosis have been unsuccessful.

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58. Bielschowsky, M., and Maas, O.: Ueber diffuse und multiple Sklerose, J. f. Psychol. u. Neurol. **44**:138, 1932.

59. Neubürger, K.: Histologisches zur Frage der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:336, 1921.

60. Urechia, C.; Mihalescu, S., and Elekes, N.: L'encéphalite periaxiale diffuse, type Schilder, Encéphale **19**:617, 1924.

61. Stewart, T.; Greenfield, J., and Blandy, M.: Encephalitis Periaxialis Diffusa, Brain **50**:1, 1927.

62. Guttmann, E.: Die diffuse Sklerose, Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:1, 1925.

63. Ferraro, A.: Histopathological Findings in Two Cases Clinically Diagnosed as Dementia Praecox, Am. J. Psychiat. **13**:883, 1934.

The combination of small and diffuse areas of sclerosis is observed not only in chronic but in acute forms. Jakob,[56] in a case of diffuse infiltrating encephalomyelitis, described small sclerotic foci in the spinal cord identical with those of disseminated sclerosis and contrasting with the diffuse process in the white matter of the brain. In addition, Jervis and I [40] recently reported a case of encephalomyelitis in which all transitions, from large, acute to small, sclerotic foci, were present in the areas of demyelinization. Small patches of demyelinization were present in the basal ganglia, the thalamus, the pons and the medulla oblongata. In the pons the small patches were in both the pes and the tegmentum (fig. 9 *A*). There were, in addition, small areas of the so-called concentric type of demyelinization.

The explanation offered by Benoit [64] for the simultaneous occurrence of areas of diffuse and of multiple sclerosis that two different diseases were associated in the same case is a difficult hypothesis to accept.

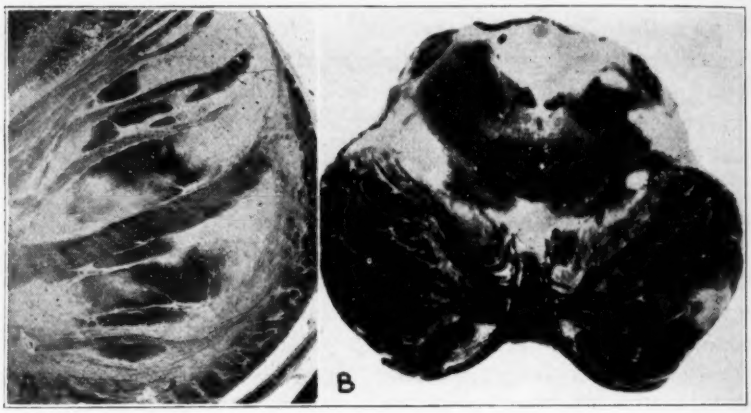

Fig. 8.—Small patches of multiple sclerosis in two cases of diffuse sclerosis. Weigert method for myelin sheaths. (*A*, after Ferraro [63] and *B*, after Gozzano and Vizioli [42]).

The aforementioned facts and considerations seem to uphold the contention that no fundamental objections exist to the unification of multiple and diffuse sclerosis.

ACUTE MULTIPLE SCLEROSIS AND ACUTE ENCEPHALOMYELITIS

In 1885 Babinski [65] devoted a chapter of his thesis on multiple sclerosis to the so-called acute form of the disease. However, he dealt

64. Benoit, W.: Zur Frage der diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:517, 1932.

65. Babinski, J.: Etude anatomique et clinique sur la sclérose en plaques, Thèse de Paris, no. 146, 1885; Recherches sur l'anatomie pathologique de la sclérose en plaques, Arch. de physiol. norm. et path. **5**:186, 1885.

more particularly with exacerbations of the process in three cases of ordinary multiple sclerosis. In the same thesis, Babinski described incidentally a variety of the condition which he termed a "destructive form of multiple sclerosis," characterized by the extreme rapidity of its course. It was not until 1904 that Marburg [31] called attention to the variety of so-called acute multiple sclerosis, which he defined as a form

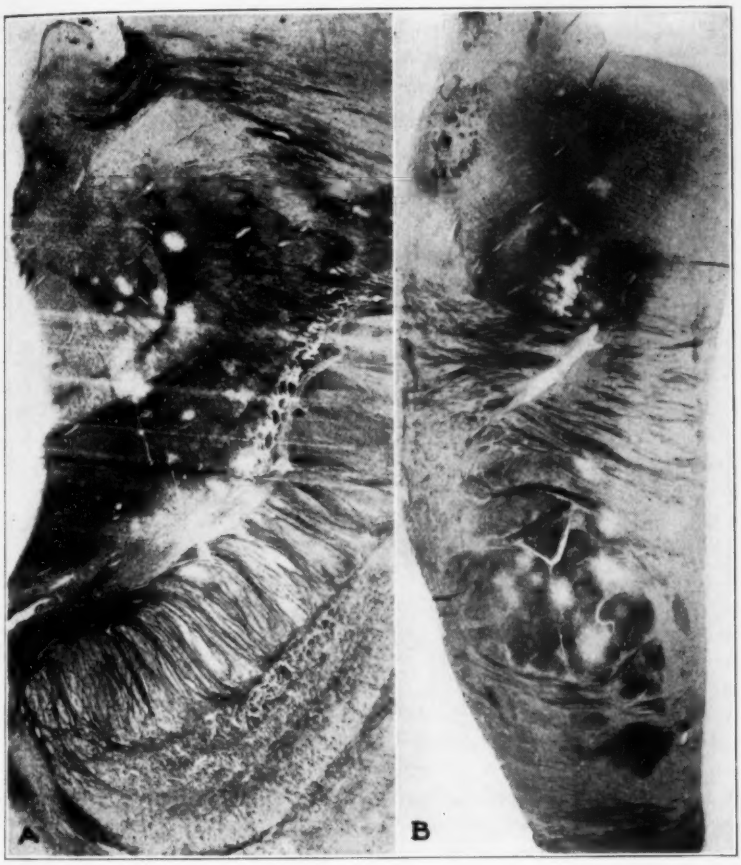

Fig. 9.—Small patches of demyelinization in a case of acute disseminated encephalomyelitis. In *A* the patches are in the thalamus and the subthalamic region; in *B*, in the pons and the tegmentum. Spielmeyer method for myelin sheaths.

of true multiple sclerosis characterized by a more rapid course. He distinguished in this condition two groups of cases: (1) those in which because of the clinical course and pathologic changes the condition deserves the qualification of "primary" acute disease, and (2) those

in which, in the course of the regular chronic process, acute lesions develop and dominate the clinical manifestations of the disease. Marburg emphasized the identity of the acute and the chronic form of multiple sclerosis and opened a debate on the two opposing views: one tending to identify multiple sclerosis with acute disseminated myelitis and encephalomyelitis and the other tending to separate the two processes.

Anton and Wohlwill,[66] though admitting that acute disseminated encephalomyelitis has a close relationship to multiple sclerosis and may be designated as its acute form, expressed the belief that it should be separated clinically and anatomically from the chronic type of multiple sclerosis. Fraenkel and Jakob [67] expressed themselves in favor of the identity of the two conditions; Oppenheim [68] rallied to their conception, though he expressed the fear that by including disseminated encephalomyelitis and myelitis in the group of multiple sclerosis the territory of the acute form of multiple sclerosis would be considerably extended. Redlich [69] and Spielmeyer [70] again advocated strongly the duality of the processes, whereas Pette [71] contributed clinical and pathologic material to the theory of unicity.

In France, Guillain and Marquézy [72] and Claude and Alajouanine [73] favored unicity, and Cournand [74] devoted an extensive and accurate study to the problem of acute mutliple sclerosis, reaching the conclusion

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66. Anton, G., and Wohlwill, F.: Multiple nicht eitrige Encephalomyelitis und multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:31, 1912.

67. Fraenkel, M., and Jakob, A.: Zur Pathologie der multiplen Sklerose mit besonderer Berücksichtigung der akuten Formen, Ztschr. f. d. ges. Neurol. u. Psychiat. **14**:565, 1913.

68. Oppenheim, H.: Der formenreichtum der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **52**:169, 1914.

69. Redlich, E.: Ueber ein gahäuftes Auftreten von Krankheitsfällen mit den Erscheinungen der Encephalomyelitis disseminata, Monatschr. f. Psychiat. u. Neurol. **64**:152, 1927.

70. Spielmeyer, W.: Der anatomische Befund bei einem 2. Fall von Pelizaeus-Merzbacherscher Krankheit, Zentralbl. f. d. ges. Neurol. u. Psychiat. **32**:203, 1923.

71. Pette, H.: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **105**:76, 1928.

72. Guillain, G., and Marquézy, R.: Le syndrome myélitique aiguë: mode de terminaision de la sclérose en plaques, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:608, 1924.

73. Claude, H., and Alajouanine, T.: Sclérose en plaques avec poussée évolutive ayant déterminé syndrome de myélite aiguë ascendante, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:609, 1924; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **38**:254, 1924.

74. Cournand, A.: La sclérose en plaques aiguë: Contribution à l'étude des encéphalo-myélites aiguës disséminées, Paris, Amédée Legrande, 1930.

that pathologically the lesions in encephalomyelitis and multiple sclerosis are comparable and that acute encephalomyelitis should be incorporated in the group of multiple sclerosis.

If one compares the symptoms outlined by Cournand [74] with the major symptoms of the common type of multiple sclerosis as described in the literature and summarized by Guillain [75] in his report on multiple sclerosis, it will be realized that the symptoms are, except for the course, fundamentally the same in both the acute and the chronic condition. In comparing the symptoms with those in acute disseminated encephalomyelitis, one again can hardly fail to recognize that they are fundamentally the same.

It is of interest that in a case clinically considered by Redlich as one of acute encephalomyelitis, typical multiple sclerosis developed later and was described as such by Pette, who had the opportunity to follow the condition clinically and to study its histologic aspects.

Pathologic Changes.—Histologically, the changes in acute multiple sclerosis and acute disseminated encephalomyelitis are identical. In both, patches of demyelinization are scattered in the spinal cord, the medulla oblongata, the cerebellum and the brain. Demyelinization may be complete or partial, and the patches may involve the white as well as the gray matter, though predominating in the white matter. Here and there the patches may appear as symmetrical. The margins of the patches are distinct, at times contrasting vividly with the surrounding normal tissue. In the midst of the patches the axis-cylinders undergo severe degenerative changes and often complete destruction. On the other hand, patches occur in which the axis-cylinders are almost intact. In the midst of the patches numerous compound granular corpuscles are generally observed free or surrounding the blood vessels. The corpuscles are generally filled with fatty disintegrated material. The number of corpuscles is proportionate to the severity of the process of disintegration. The blood vessels are generally dilated and surrounded by lymphocytes and plasma cells or compound granular corpuscles or a combination of all these elements. The relationship of the patches to the blood vessels is not essential.

Glia cells undergo hypertrophy and hyperplasia, particularly at the periphery of the patches, where numerous elements with thick, long processes occur. In the midst of the patches protoplasmic glia cells also show hypertrophy, sometimes recalling the aspect of *gemästete* or monster cells. These cells do not differ from the cells described in numerous cases of diffuse sclerosis (fig. 10). Glia fibrils occur both in the patches and at their periphery. The intensity of the glia fibrillar

75. Guillain, G.: Rapport sur la sclérose en plaques, Rev. neurol. **31**:648, 1924.

reaction depends on the age of the patch; the older the patch the stronger the glia network. The microglia reaction is also pronounced in the sense of hyperplasia and transformation of the cellular elements into compound granular corpuscles. The meninges occasionally disclose lymphocytic infiltration.

Perivascular infiltration in the areas of demyelinization depends on the intensity of the process, the exudate being almost absent in very small patches. It is of importance to note that in many cases of both acute multiple sclerosis and acute disseminated encephalomyelitis there has been reported definite involvement of the optic nerves, the optic chiasm or the optic tract. The pathologic process involving the optic system is identical with that in the spinal cord or in the brain and

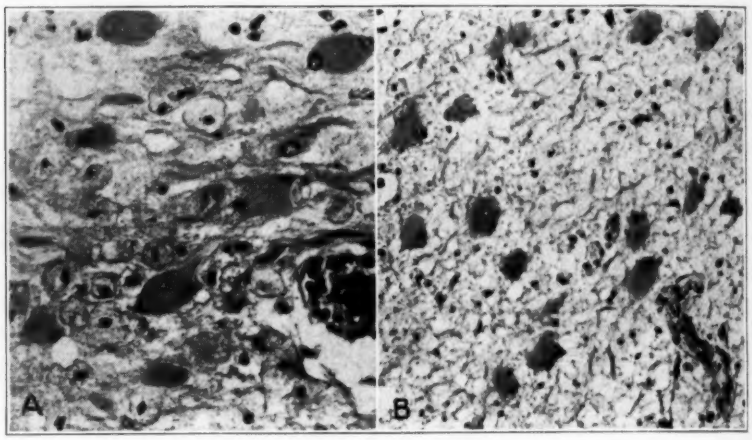

Fig. 10.—*Gemästete* neuroglia cells in (*A*) a case of diffuse sclerosis and (*B*) a case of acute disseminated encephalomyelitis. Hematoxylin and eosin stain.

consists fundamentally of demyelinization, involvement of the axis-cylinders and progressive glial reaction. Small areas of necrosis in the white matter have been described in some instances.

Altogether, this review of the clinical and pathologic features of multiple sclerosis, both in its acute and in its chronic form, and of acute disseminated encephalomyelitis justifies one in subscribing to Pette's opinion that neither clinical nor histopathologic observations establish a distinction between multiple sclerosis and disseminated encephalomyelitis. Whatever variation in the histopathologic process has been described can be explained on the basis of the intensity and duration of the pathologic process, associated with the age and resistance of the patient.

OPHTHALMONEUROMYELITIS (DEVIC'S DISEASE)

I shall now discuss the right to autonomy as a clinicopathologic entity of so-called ophthalmoneuromyelitis, or acute optic neuromyelitis.

The association of optic manifestations with diseases of the spinal cord is not a new discovery; as early as 1870 Clifford Allbutt [76] first described ophthalmologic signs in the course of spinal disease. Dreschfeld [77] described two cases of acute myelitis associated with optic neuritis. Devic [78] described acute dorsolumbar myelitis associated with optic neuritis. He also inspired Gault's [79] thesis on acute optic neuromyelitis. Since, the condition has been known as Devic's disease.

Is this a clinicopathologic entity? Is it not rather the same fundamental process of acute multiple sclerosis, in which involvement of the optic nerves and the optic tract is somewhat more pronounced? On the basis of the thesis of Michaux,[80] who collected most of the reported cases of ophthalmoneuromyelitis up to 1930, and from study of material at the New York State Psychiatric Institute and Hospital, I have analyzed the clinical manifestations. Comparison of these clinical manifestations with those of acute multiple sclerosis and acute disseminated encephalomyelitis shows striking similarities and do not justify the labeling of Devic's disease as a separate clinical entity.

PATHOLOGIC CHANGES

Neuromyelitis is characterized fundamentally by demyelinization, destruction of the axis-cylinders and reactive gliosis. The demyelinization generally invades the spinal cord, sometimes in more than one segment, thus producing an association of primary and secondary degenerations. Study of an involved segment of the spinal cord reveals the presence of diffuse areas of demyelinization, most of them involving only the white matter but some also the gray matter.

The process of disintegration may at times appear somewhat more intense than that in acute multiple sclerosis, the process having at times a tendency toward necrosis. This tendency is not, however, an absolute characteristic, cases having been described in which the demyelinization

76. Allbutt, T.: On the Ophthalmoscopic Signs of Spinal Disease, Lancet **1**:76, 1870.

77. Dreschfeld, J.: On Two Cases of Acute Myelitis Associated with Optic Neuritis, Lancet **1**:8, 1882.

78. Devic, E.: Myélite aiguë dorso-lombaire avec névrité optique, Cong. franç. de méd. **1**:434, 1895.

79. Gault, F.: De la neuromyélite optique aiguë, Thèse de Lyon, no. 981, 1894.

80. Michaux, L.: La neuro-myélite optique aiguë, Paris, Libraire Louis Arnette, 1930.

was not different from that described in disseminated sclerosis (fig. 11) (Cestan, Riser and Planques [81]).

The axis-cylinders are destroyed in proportion to the intensity of the pathologic process, the less involved areas disclosing a larger proportion of well preserved axis-cylinders, in contrast with the considerable destruction of these structures in areas with necrotic tendencies.

Fig. 11.—Aspects of demyelinization in another case of optic neuromyelitis in which the authors stressed the absence of necrotic tendencies and the similarity to the sclerotic areas of multiple sclerosis. Weigert method for myelin sheaths (after Cestan, Riser and Planques [81]).

In the foci of demyelinization there is the same accumulation of compound granular corpuscles loaded with various amounts of fat and

81. Cestan, Riser and Planques: De la neuro-myélite optique, Rev. neurol. **2:** 741, 1934.

products of disintegration (Barrera [82]). As in acute disseminated encephalomyelitis and acute multiple sclerosis, the compound granular corpuscles occur either free or surrounding the blood vessels. Here also, the blood vessels appear dilated and surrounded by a collar of cellular elements, which vary from case to case. In some instances compound granular corpuscles are the only elements in the patches; in others lymphocytes and plasma cells constitute the predominant elements, while in still others groups of lymphocytes and compound granular corpuscles are observed.

The glial reaction does not vary from that in acute multiple sclerosis and disseminated encephalomyelitis.

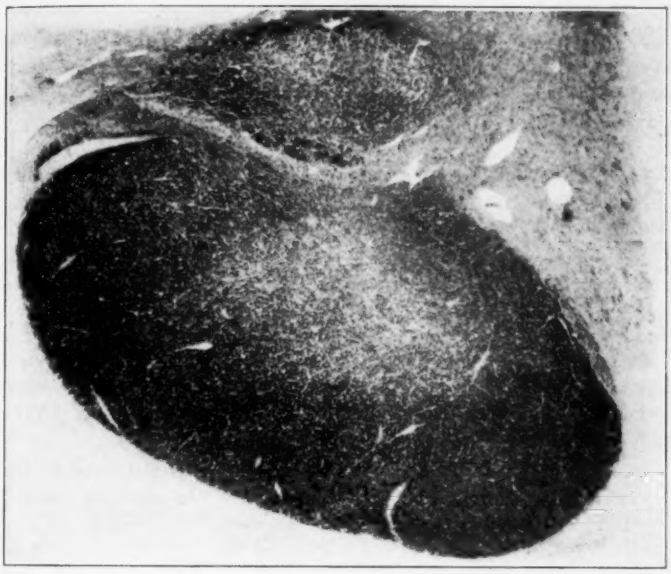

Fig. 12.—Demyelinization of the optic nerves in a case of ophthalmoneuromyelitis. Weigert method for myelin sheaths.

Study of the optic system discloses histopathologic changes identical with those in cases of acute disseminated encephalomyelitis, with the possible difference that in ophthalmoneuromyelitis the changes may be slightly more severe in some instances (fig. 12).

The clinical and pathologic changes in ophthalmoneuromyelitis do not contain elements strong enough to establish either a clinical or a pathologic difference between acute multiple sclerosis, acute disseminated encephalomyelitis and ophthalmoneuromyelitis. The differences

82. Barrera, S. E.: Ophthalmo-Encephalo-Myelopathy, Psychiatric Quart. **6**:421, 1932.

related to the age and the localization and distribution of the pathologic process being taken into account, the conditions constitute a similar fundamental clinicopathologic unit.

The fact, demonstrated by Michaux, that the lesions in ophthalmoneuromyelitis have a necrotic tendency and therefore should be differentiated from those of acute disseminated encephalomyelitis does not seem of sufficient importance, for the following reasons: (1) Subjective elements appear in describing the necrotic tendency of areas of demyelinization; (2) typical cases of optic neuromyelitis have been described in which there was no necrotic tendency of the lesions, and (3) cases of acute encephalomyelitis are observed in which there is a necrotic character of the lesions.

In connection with the relationship between ophthalmoneuromyelitis and multiple sclerosis, I may mention the case of van Bogaert,[83] who in 1927 presented before the Société de neurologie of Paris a patient with a disease diagnosed as acute optic neuromyelitis.

> The clinical diagnosis was based on the coexistence of bilateral retrobulbar neuritis and flaccid paraplegia, both developing in the course of a few hours and accompanied by fever. At the end of the fortieth day the patient began to improve gradually.
>
> A year later, the patient had a fresh exacerbation of the process; headache and vomiting became intense; vision diminished rapidly, and the gait became uncertain. Slight nystagmus appeared. Paraplegia became quadriplegia, flaccid in nature, with disturbances of the sphincters, gross involvement of sensation and decubitus. In the course of the next two years symptoms of cerebellar involvement appeared and were followed by death. The diagnosis of multiple sclerosis was advanced.
>
> Histopathologically, there were large areas of demyelinization in the white substance, particularly around the lateral ventricles. In addition, small patches typical of multiple sclerosis were present in the medulla oblongata, the cerebellum and the pons. There were also primary areas of demyelinization in the posterior and the lateral columns of the spinal cord. Demyelinization was also present in the optic chiasm and in both optic nerves.

In van Bogaert's estimation, the original diagnosis was an error, the case having proved to be one of typical multiple sclerosis. I do not subscribe to his opinion of an initial error and report this case to document the impossibility at times of differential diagnosis between optic neuromyelitis and acute multiple sclerosis.

From the clinical standpoint, it is also of interest to recall here the case described by Catola.[84]

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83. van Bogaert, L.: Erreur de diagnostic: neuromyélite optique aiguë, premier stade d'une sclérose en plaques typique, J. de neurol. et de psychiat. **32**:234, 1932.

84. Catola, S.: Sur le début de la sclérose en plaques, Rev. neurol. **1**:687, 1924.

In a young woman there developed acute retrobulbar neuritis leading to amaurosis in eight days, associated with complete paraplegia, complete loss of deep reflexes and disturbance of the sphincters. The course of the disease was benign; after a month the patient had made a full recovery without any specific treatment. Twelve months later there developed gradually an ataxic, spasmodic gait with increased deep reflexes, a suggestion of the Babinski sign, nystagmus and intention tremor. The Wassermann reaction was negative.

With respect to the relationship of ophthalmoneuromyelitis to diffuse sclerosis of the brain, I may recall the existence of transitory forms between pure ophthalmoneuromyelitis and ophthalmoneuromyelitis in association with partial or diffuse involvement of the brain tissue. I shall cite, therefore, the case reported by Guillain, Alajouanine, Bertrand and Garcin,[35] which was later discussed by Michaux, in which, associated with lesions typical of ophthalmoneuromyelitis, there was a large necrotic area involving a considerable portion of the hypothalamic region. Mention should also be made of the cases of Barrera [82] and of Cestan, Riser and Planques [81] in which, associated with lesions of the spinal cord typical of ophthalmoneuromyelitis, areas of demyelinization were also present in the brain stem, the cerebellum and the white matter of the cerebrum (fig. 13). Finally, I may recall the case described by Marinesco, Draganesco and their co-workers in which, associated with typical necrotic lesions of the spinal cord, diffuse symmetrical sclerosis was present in the white matter of the brain.

It seems, therefore, that both clinical and pathologic considerations point to a close relationship of the processes of diffuse sclerosis, multiple sclerosis, acute encephalomyelitis and ophthalmoneuromyelitis.

SUBACUTE NECROTIC MYELITIS

As first described by Foix and Alajouanine [85] in 1926, subacute necrotic myelitis seemed to constitute a process which has little in common with the demyelinating processes of the central nervous system. However, the mention in their second case of a certain degree of papillitis with reduction of vision to two-thirds normal acuity raised the question of the relationship of this type of necrotic myelitis to so-called ophthalmoneuromyelitis. Subacute necrotic myelitis has been considered by Foix and Alajouanine as forming a clinicopathologic entity with the following clinical characteristics:

1. Progressive, amyotrophic paraplegia, originally spastic and later flaccid, the spastic phenomena progressing toward a higher level, with flaccidity and amyotrophy replacing spasticity from the lower to the higher levels.

2. Sensory disturbance, first of dissociated type and later becoming more and more global and following with a certain delay the progress of the amyotrophic and paralytic phenomena.

85. Foix, C., and Alajouanine, J.: La myélite nécrotique subaiguë, Rev. neurol. **2**:1, 1926.

3. Albuminocytologic dissociation of the cerebrospinal fluid; hyperalbuminosis and moderate or slight lymphocytosis.

4. A subacute course leading to death within one or two years.

Pathologic Change.—The condition corresponds to myelitis, with necrotic tendencies predominating in the gray matter but extending to

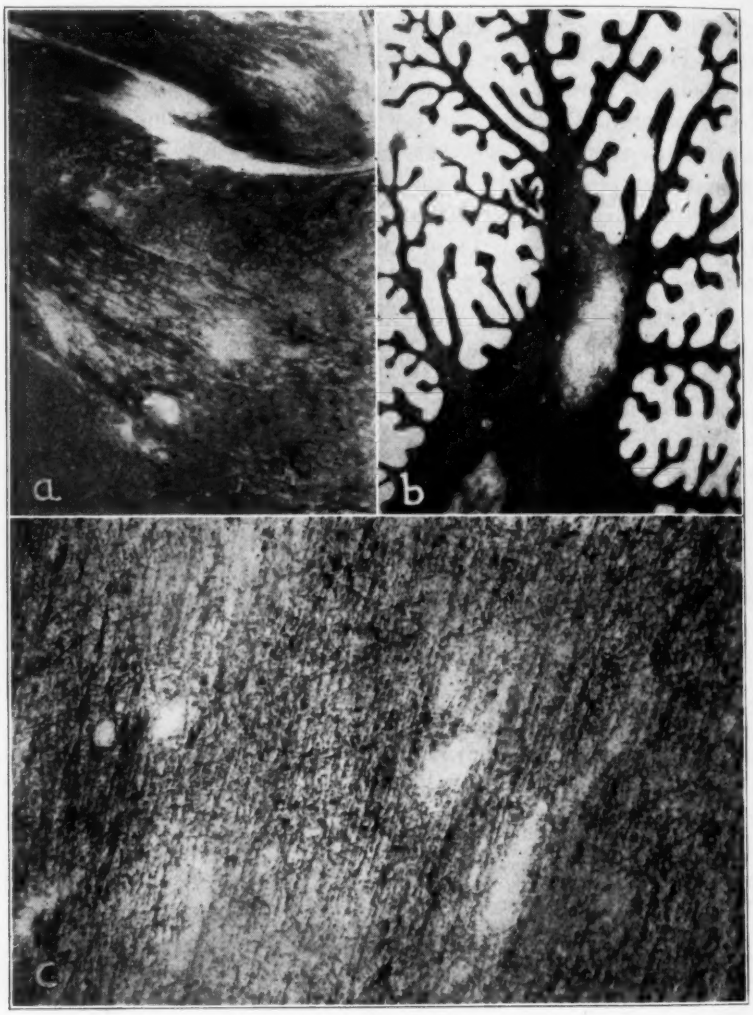

Fig. 13.—Demyelinization of the white matter of the cerebrum and the cerebellum in cases of ophthalmoneuromyelopathy (*A* and *B*, after Cestan, Riser and Planques,[81] and *C*, after Barrera [82]).

the white matter. Myelitis, which is particularly destructive at the level of the lumbosacral enlargement, decreases gradually in intensity at higher levels, to disappear at about the middle of the dorsal region of

the cord. The condition is accompanied by endomesovascularitis which, though not reaching the brain, involves both intramedullary and extramedullary blood vessels. The endomesovascularitis results in considerable hypertrophy of the blood vessels, differing in aspect from syphilitic vascularitis.

The pathologic aspect in conjunction with the remarkable clinical course constitutes, according to Foix and Alajouanine, a characteristic entity. Autopsy in the second case revealed no demyelinization in the optic system.

In 1930 van Bogaert, Ley and Brandes [86] described a case of myelitis accompanied by sensory and amyotrophic disturbances.

At the beginning there were myoclonic twitchings of the abdominal muscles and complete insomnia. In a few weeks the sensory changes diminished in intensity, but violent pains in the territory of the trigeminal nerve appeared. At that time, in 1928, a diagnosis of epidemic encephalitis of a lower type was made, the *forme basse* of French authors. Six months later, for the first time ocular symptoms appeared—loss of vision in the right eye. The fundi, however, were normal. Eight days later loss of vision occurred in the left eye—complete blindness, with no changes in the fundi. Death occurred in March 1928, and histologic study resulted in a change in diagnosis to subacute necrotic myelitis.

The interest in van Bogaert's case lies, however, in the fact that, in addition to the medullary changes, definite areas of demyelinization were present in the cerebellum, the medulla and the pons. In the cortex of the brain cerebral perivascular infiltration and meningeal reactions were also reported. The changes of the blood vessels were not as marked as those reported by Foix and Alajouanine and consisted of only a moderate degree of progressive change, particularly of the media, the intima being intact. In addition, there was considerable hyalinization of the walls of the blood vessels.

Because of the concomitant lesions of the spinal cord and the brain it is natural to consider this case as one of a transition between the subacute necrotic myelitis of Foix and Alajouanine and the group of demyelinating processes of the central nervous system.

In support of this contention, I may mention a case reported by Marinesco, Draganesco and their associates,[87] in which the interesting histopathologic features were:

1. Presence of necrotic changes in the lumbosacral region of the cord leading to cavity formation in the right posterior column. In the sacral region of the cord the necrotic changes were pronounced in the posterior column. No hypertrophic changes were present in the walls of the blood vessels (fig. 14).

86. van Bogaert, L.; Ley, R. A., and Brandes, F.: Contribution anatomo-clinique à l'étude de la myélite nécrotique subaiguë de Foix-Alajouanine, Rev. neurol. **2**:1, 1930.

87. Marinesco, G.; Draganesco, S.; Sager, O., and Grigoresco, D.: Sur une forme particulière anatomo-clinique d'ophthalmo-neuromyélite, Rev. neurol. **2**:193, 1930.

2. Presence of diffuse areas of demyelinization in the brain, presenting characteristics typical of the demyelinization described in multiple and diffuse sclerosis (fig. 15).

3. Intense demyelinization of the chiasm.

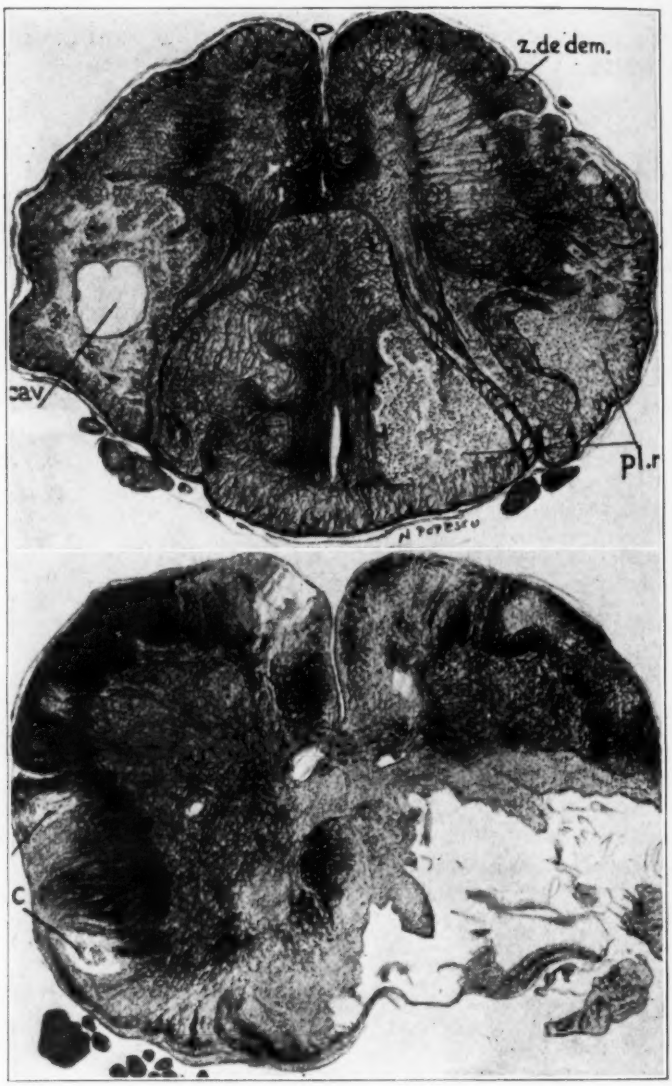

Fig. 14.—Considerable necrosis of the tissue of the spinal cord, leading to formation of cavities in a case of ophthalmoneuromyelitis (after Marinesco, Draganesco, Sager and Grigoresco [87]).

The combination of hypertrophic changes and marked hyaline degeneration of the walls of the blood vessels in the case of van Bogaert and

Ley reminds me of other sporadic or familial cases of diffuse sclerosis in which hyaline changes have been reported in the blood vessels. In this connection I may recall the case of "atypical diffuse sclerosis" described by Löwenberg and Fulstow,[88] in which the pathologic process was characterized mainly by demyelinization with a tendency toward necrosis, as a result of which the process of repair was performed by glial elements in association with connective tissue, with later hyaline degeneration. In this case there was, in addition, severe hyaline degeneration of the blood vessels of both the meninges and the brain substance, leading to thickening of the walls of the blood vessels, gradual reduction and occasionally occlusion of the vessels (fig. 16).

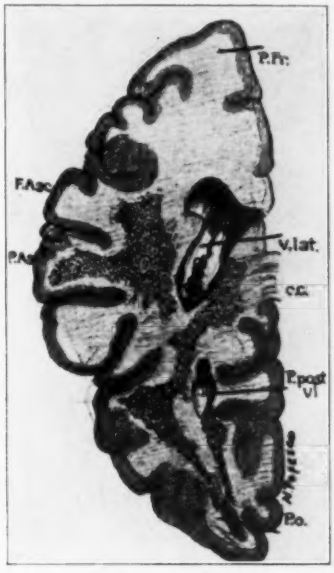

Fig. 15.—Schematic representation of the large areas of demyelinization in the white substance of the brain in the case of ophthalmoneuromyelitis with necrosis of the spinal cord lesions which are shown in figure 14 (after Marinesco and others [87]).

The histopathologic changes in the original cases of Foix and Alajouanine and in the later cases of van Bogaert, Ley and Brandes, and Marinesco, Draganesco and their associates, in which the necrotic changes of the cord were associated with demyelinization of the brain, suggest that subacute necrotic myelitis may be classified under the general heading of demyelinating processes of the central nervous system.

88. Löwenberg, K., and Fulstow, M.: Atypical Diffuse Sclerosis, Arch. Neurol. & Psychiat. **27**:389 (Feb.) 1932.

The case of Marinesco and his associates is particularly instructive because it shows distinctly the association of necrotic features in the spinal cord with what the authors term Schilder's disease in the brain.

DEMYELINATING PROCESSES FOLLOWING ACUTE INFECTIOUS DISEASES OF CHILDHOOD

It is well known that the fundamental lesion in some forms of encephalitis following the common infectious diseases of childhood is a process of perivascular demyelinization. In cases of encephalitis following or accompanying measles, varicella, smallpox, some forms of rubella, influenza and vaccinia, the main histopathologic features, which Scheffer and I [89] reported elsewhere, consist of: (1) perivascular demye-

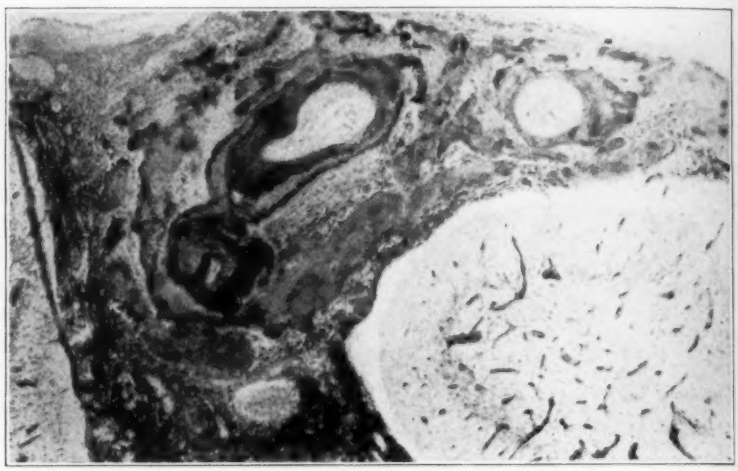

Fig. 16.—Severe hyaline degeneration of the cerebral blood vessels in a case of so-called atypical sclerosis (after Löwenberg and Fulstow [88]). Nissl stain.

linization (fig. 17), (2) perivascular proliferation of microglial elements (fig. 18), and (3) moderate progressive gliosis.

The demyelinization, though involving mainly perivascular areas, may be present here and there apparently independent of a blood vessel. A study by serial sections of the area, however, shows most often the relationship of the area to an underlying blood vessel. The demyelinization is not limited to the brain tissue but spreads to the pons, the cerebellum, the medulla and the spinal cord; there symmetrical lesions

89. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles: A Pathologic Report of Six Cases, Arch. Neurol. & Psychiat. **25**:748 (April) 1931.

are observed, some of which follow the course of the main septums of the cord. In the brain the subependymal region shows a predilection for the lesions, just as it does for the lesions of acute multiple sclerosis and acute disseminated encephalomyelitis.

The blood vessels are generally surrounded by a considerable reaction of the microglia cells, with a definite tendency toward the formation of compound granular corpuscles. Occasionally, among the microglia cells lymphocytes and even plasma cells are observed. The dominant character of the perivascular proliferation is one, however, of proliferating microglial elements.

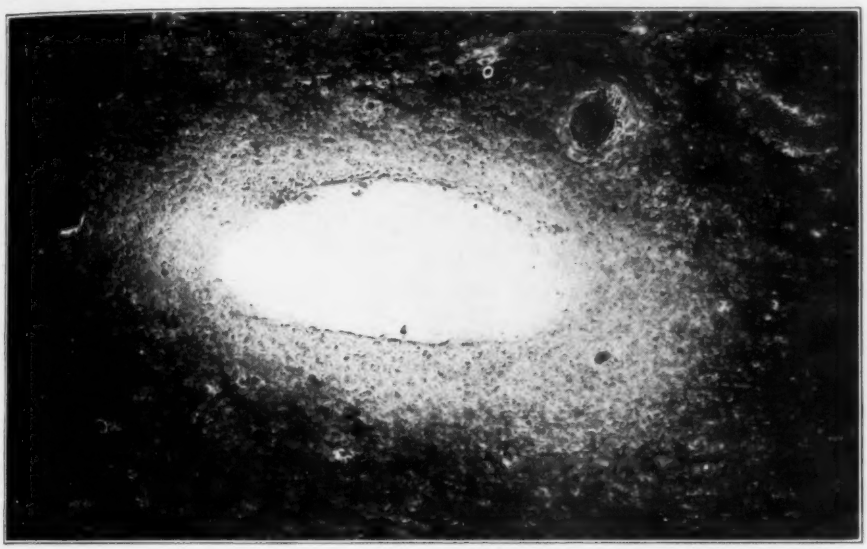

Fig. 17.—Perivascular area of demyelinization in a case of encephalitis following measles. Spielmeyer method for myelin sheaths.

The axis-cylinders participate in the pathologic process; all kinds of degenerative aspects of these structures are encountered, from primary swelling to complete fragmentation and disintegration.

The reaction of the neuroglia, though only slightly pronounced because of the early stages of the reaction, consists of changes of both regressive and progressive nature, with the latter predominating. In some areas Holzer's stain reveals reactive gliosis. The glial proliferation is likely to proceed actively in chronic stages, and the process may be represented by diffuse sclerosis, as in the case of Gagel,[54] in which diffuse demyelinization and replacement with glial tissue followed an infection with measles in a child.

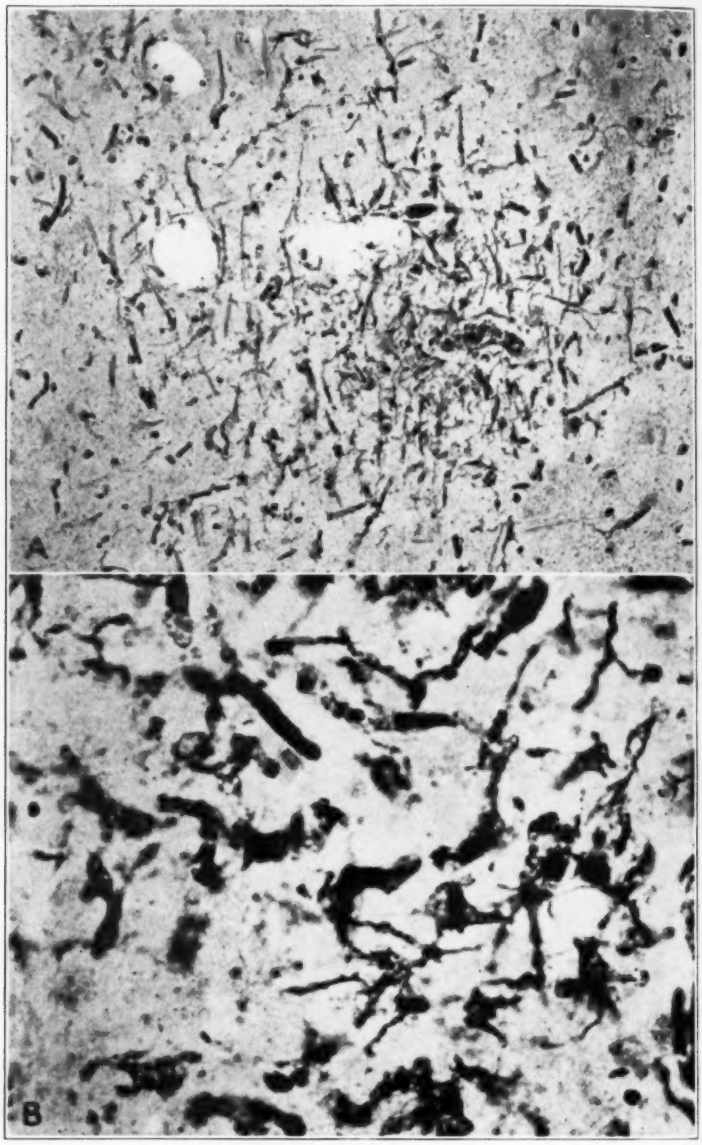

Fig. 18.—Perivascular proliferation of microglia cells as seen (*A*) with low power and (*B*) with high power, showing the transformation of some of the microglia cells into compound granular corpuscles. Hortega's silver carbonate method.

The histopathologic changes thus described were denominated by Marsden and Hurst [90] "acute perivascular myelinoclasis." They expressed the belief that the lesions may occur even in the absence of exanthematous conditions, appearing therefore as an independent disease. In support of their contention they quoted Turnbull [91] as stating that there can be no doubt that a condition resembling vaccinal encephalitis has occurred independent of recent vaccination and observed exanthem. They also quoted Küssner and Brosin,[92] who described identical changes in a man who had suffered for a year from chronic gonorrhea. The lesions observed in the cord in the first case of Francotte [93] appeared to be similar, while Krabbe [12] described changes in the brain. Similar, but more chronic, changes were described by Dreschfeld.[77] Wohlwill [94] observed changes identical with those in postvaccinal encephalitis in a patient not suffering from any known infectious disease. Marsden and Hurst asserted that "acute perivascular myelinoclasis" is entitled to recognition as an independent clinicopathologic entity.

DEMYELINATING PROCESSES IN DEFICIENCY DISEASES (PERNICIOUS ANEMIA, AVITAMINOSIS?)

Though the data available at present are scanty, there is a tendency to consider the demyelinization occurring in cases of pernicious anemia and pellagra as a primary type resulting from deficiency in certain vitamins.

In favor of this conception is the recent work of Zimmerman and Burack,[95] who in adult dogs maintained on an artificial balanced ration, adequate, as far as was known, in all dietary essentials except vitamin B_2 (G), observed that after a sufficient time there developed a slowly progressive disease characterized by loss of weight, persistent vomiting and diarrhea and marked muscular weakness, which ended fatally in from 200 to over 300 days. The histologic changes consisted of demyelinization of the peripheral nerves and the posterior columns

90. Marsden, J. P., and Hurst, E. W.: Acute Perivascular Myelinoclasis ("Acute Disseminated Encephalomyelitis") in Smallpox, Brain **55**:181, 1932.

91. Turnbull, H.: Encephalo-Myelitis in Virus Diseases and Exanthemata, Brit. M. J. **2**:331, 1928.

92. Küssner, B., and Brosin, F.: Myelitis acuta disseminata, Arch. f. Psychiat. **17**:239, 1886.

93. Francotte, X.: Etudes sur l'anatomie pathologique de la moelle épinière, Arch. de neurol. **20**:46, 1890.

94. Wohlwill, F.: Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

95. Zimmerman, H. M., and Burack, E.: Lesions of the Nervous System Resulting from a Deficiency of the Vitamin B Complex, Proc. Soc. Exper. Biol. & Med. **28**:645 (March) 1931; Arch. Path. **13**:207 (Feb.) 1932.

of the spinal cord, particularly the fasciculus gracilis, and less often the anterior columns. Occasionally, slight degenerative changes were noticed in most of the fiber tracts of the cord. Gliosis followed demyelinization.

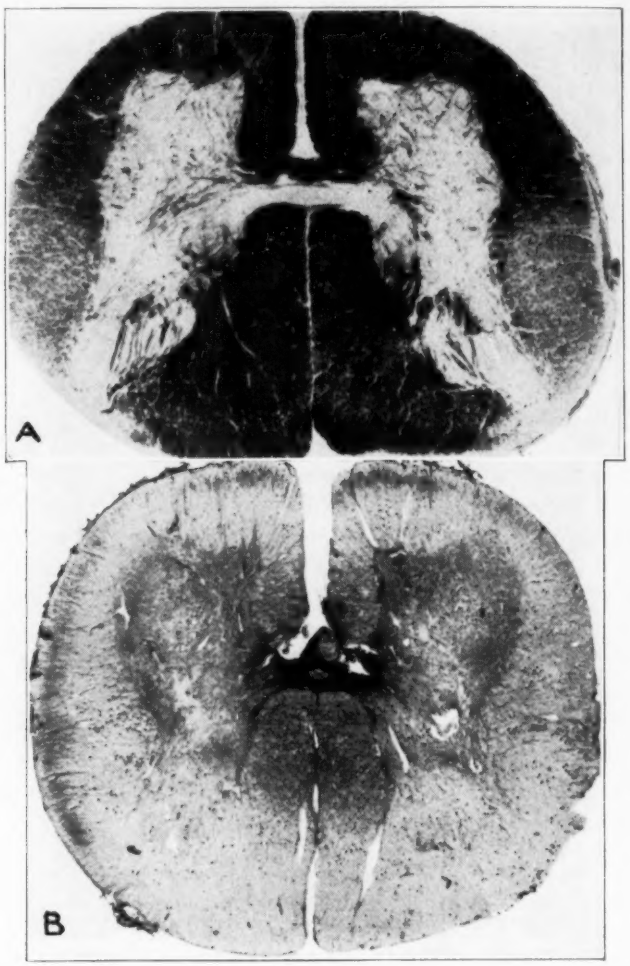

Fig. 19.—(*A*) Demyelinization in the spinal cord in a case of human pellagra, showing the slight demyelinization of the posterior columns (Weigert method for myelin sheaths). In *B* gliosis is seen in both the gray and the white matter; in the latter no correspondence exists between the demyelinated areas and the gliosis (Holzer method for glia fibrils).

Gildea, Kattwinkle and Castle[96] had already reported in dogs fed a diet deficient in both the antineuritic and the pellagra-preventing

96. Gildea, E.; Kattwinkle, E., and Castle, W.: Experimental Combined System Disease, New England J. Med. **202**:523, 1930.

portions of vitamin B the occurrence of patchy demyelinization of the spinal cord, which they compared with lesions encountered in association with combined system disease in man.

Zimmerman and Burack also mentioned the similarity of the lesions to those frequently described in cases of pellagra (fig. 19) and malnutrition in man (Pentschew,[97] Winkelman[98] and Sundwall and Francis[99]). If one considers the analogy of the changes described in pellagra and malnutrition with those in pernicious anemia, one sees the importance of the correlation. A closer link between the pathogenesis of pellagra and that of pernicious anemia has recently been advocated by Strauss and Castle,[100] who hypothecated that pernicious anemia is due to the lack of a specific hematopoietic reaction between an extrinsic factor (vitamin B_2) and an intrinsic factor of normal human gastric juice.

EXPERIMENTAL DEMYELINIZATION DUE TO KNOWN TOXIC OR FOREIGN AGENTS

Experimental pathologic studies have shown the possibility of reproducing demyelinization in various types of animals after the use of various nontoxic substances. Thus, tetanus toxin has been used by Claude[101] and Putnam, McKenna and Morrison[102] in a successful attempt to reproduce demyelinization in animals. The toxins of Aspergillus fumigatus (Ceni and Besta[103]), saponin (Donaggio[104]), vinilamine (Luzzato and Levi[105]), bile (Weil and Crandall[106]) and potas-

97. Pentschew, A.: Ueber die Histopathologie des Zentralnervensystems bei der Psychosis pellagrosa, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:17, 1928.

98. Winkelman, N.: Beiträge zur Neurohistopathologie der Pellagra, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926.

99. Sundwall, J., and Francis, E.: Studies in Pellagra, United States Public Health Service Hygienic Laboratory Bulletin 106, 1917, p. 5.

100. Strauss, M., and Castle, W.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, New England J. Med. **207**:55, 1932.

101. Claude, H.: Myélite experimentale sub-aiguë par intoxication tetanique, Arch. de physiol. norm. et path. **29**:843, 1897.

102. Putnam, T.; McKenna, J., and Morrison, L.: Studies in Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931.

103. Ceni, C., and Besta, C.: Sclerosi in placche sperimentale, da tossici aspergillari, Riv. sper. di freniat. **31**:125, 1905.

104. Donaggio, C. R.: Sur le parkinsonisme postencéphalitique: Une doctrine cortico-nigrique, Rev. neurol. **32**:1058, 1925.

105. Luzzato, R., and Levi, A.: L'action de la vinilamine sur le system nerveux, Arch. internat. pharmacodyn. et de thérap. **26**:5, 1932.

106. Weil, A., and Crandall, L.: Die Beziehung zwischen dem Lipenasegehalt und der neurotoxischen Wirkung des Serums nach experimenteller Leberschädigung, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:577, 1932.

sium cyanide (Ferraro [41] and Rubino [107]) have been used successfully in the experimental production of demyelinization followed in some instances by a typical glial reaction, as in my experiments (fig. 20).

In some instances the experimental lesions thus produced did not differ histologically from lesions in acute or chronic multiple sclerosis. The analogies are so striking that Putnam spoke of experimental multiple sclerosis.

In my experiments the reproduction of demyelinization in both the brain and the spinal cord following the use of potassium cyanide, the severe involvement of the axis-cylinders, the considerable reactive gliosis and the occurrence of occasional softenings have undoubtedly close analogies with the same changes in cases of diffuse sclerosis in man. Even the symmetry of the demyelinization, which is extensive and invades the white substance of the hemisphere and the brain stem, the cerebellum, the pons, the medulla and the spinal cord, is comparable with that which occurs in many cases of diffuse sclerosis. The process in the experimental material is fundamentally degenerative.

I must mention here the experimental work of Rivers and Schwentker,[108] who succeeded in inducing encephalomyelitis accompanied by destruction of myelin in monkeys. These authors succeeded with repeated intramuscular injections of aqueous emulsions and alcohol-ether extracts of sterile normal brains in producing pathologic changes accompanied by destruction of myelin in the brains of seven of eight monkeys (Macacus rhesus). Eight monkeys used as controls remained well. Cultures of material from the involved brains remained sterile, and no agent was transmitted by means of intracerebral inoculations of monkeys, rabbits, guinea-pigs and white mice with the emulsion of bits of the brains.

SPONTANEOUS DEMYELINIZATION IN ANIMALS (MONKEYS)

After Schob's [109] report of demyelinization in the orang-utan, Scherer [110] described the occurrence in five baboons (Papio hamadryas

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107. Rubino, A.: Alterazioni della mielina da tossici, Riv. di pat. nerv. **45**: 191, 1935.

108. Rivers, Thomas M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Induced in Monkeys, J. Exper. Med. **61**:689, 1935.

109. Schob, F.: Disseminierte, konfluirende Sklerose des Hemisphärenmarklagers des Affen kombiniert mit systematischer Erkrankung des Sehnerven sowie der Hinterwurzeln und Hinterstränge, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**: 95, 1931.

110. Scherer, H.: Funikuläre Spinalerkrankungen mit schwerer Beteiligung des Grosshirnmarkes und Opticusveränderungen bei fünf Pavianen, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:212, 1932.

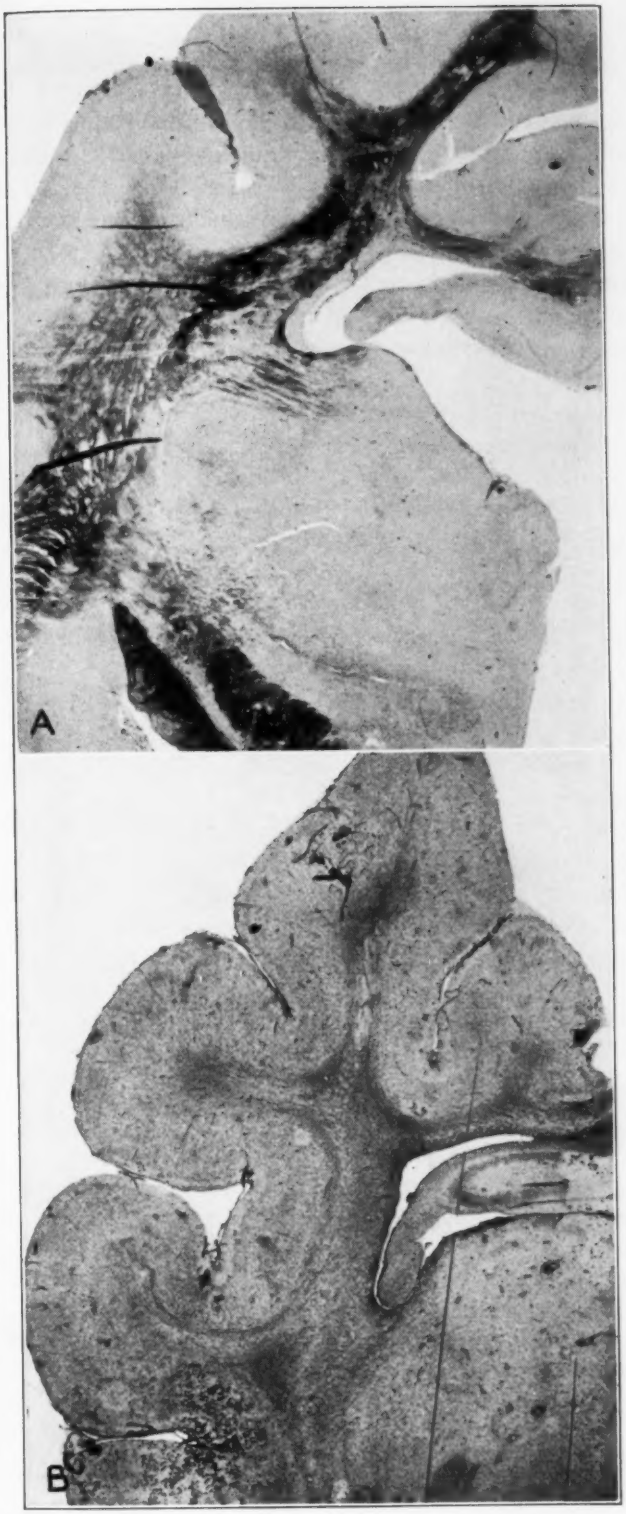

Fig. 20.—(*A*) Diffuse demyelinization in the white substance of the hemisphere of a cat poisoned with potassium cyanide and demyelinization of the optic tract (Spielmeyer method for myelin sheaths). (*B*) Corresponding gliosis in the demyelinated areas (Holzer method for glia fibrils).

L) of a spontaneous process of demyelinization, which involved the white substance not only of the cerebral hemisphere but of the spinal cord and the optic tract. The occurrence of such demyelinization has been reported at the same time by Gartner [111] and later, in the United States, by Davison [112] (fig. 21).

Of interest are the analogies which Scherer established between his observations and those in cases of pernicious anemia in man. Davison, because of the demyelinization, was inclined to consider the similarity

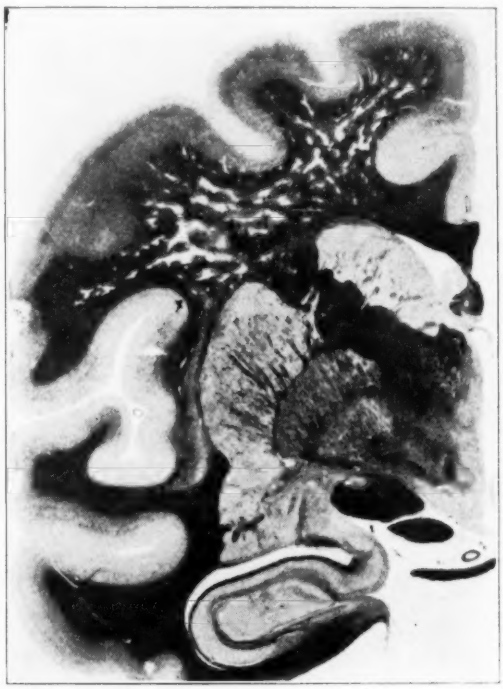

Fig. 21.—Demyelinization in the hemisphere of a baboon (Papia cynocephalus) (after Davison [112]). Spielmeyer method for myelin sheaths.

to the changes which he and Keschner [113] described in cases of toxic myelopathy in man.

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111. Gartner, M., quoted by Scherer.[110]

112. Davison, C.: Disseminated Demyelinization of the Central Nervous System in Monkeys, and Allied Disorders in Man, J. Neurol. & Psychopath. **14**:227, 1933.

113. Davison, C., and Keschner, M.: Myelitic and Myelopathic Lesions (a Clinicopathologic Study): II. Toxic Myelopathy, Arch. Neurol. & Psychiat. **29**: 600 (March) 1933.

DISSEMINATED ENCEPHALOMYELITIS IN THE DOG (NERVOUS FORM OF CANINE DISTEMPER)

Pugh [114] and Perdrau and Pugh [115] summarized the clinical and pathologic characters of disseminated encephalomyelitis in the dog. From their description it appears that the disease is protean in its clinical aspects but can often be divided into a primary and a secondary stage. In the primary stage, which usually lasts from a few days to three weeks, there is an abrupt onset with shivering and elevation of temperature, followed by a lower degree of intermittent fever, conjunctivitis, muscular pains, tenderness on manipulation of the neck or the lumbar region and frequent gastro-intestinal derangements. In the secondary stage definite symptoms due to involvement of the brain or the spinal cord become manifest. The principal features of this stage of nerve involvement, according to Perdrau and Pugh, are convulsions, paresis of one or more limbs, nystagmus, lethargy, psychic symptoms, possibly due to hallucinations, comparatively little fever, myoclonus and a tendency to remissions followed by relapses. Complete recovery is not common.

Histologically, the striking microscopic change is mononuclear infiltration of the meninges and some of the perivascular spaces in the nerve parenchyma. The white and the gray matter are equally affected. In the vast majority of cases the most severe inflammatory changes are shown in and around the pons, the medulla and the peduncles of the cerebellum. By far the most interesting pathologic change is demyelinization of a type reminiscent of that in acute or subacute disseminated sclerosis in man. This is observed chiefly in the peduncles or the folia of the cerebellum or in the arcuate fibers. The most recent of these lesions occasionally approximate the type which is observed in subacute disseminated sclerosis and the acute disseminated encephalomyelitis which occasionally follows vaccination, measles and other infections; the demyelinization is associated with one or more small vessels, the walls of which are thickly infiltrated with mononuclear cells.

Demonstration of the microglia by Hortega methods was found by Perdrau and Pugh to be more difficult in the dog than in the rabbit or in man. Neuroglial hypertrophy, on the other hand, was much better demonstrated by the appropriate method of Hortega. Patches of demyelinization were observed in the spinal cord in one of four cases in which examination was made. The patches showed a tendency toward sym-

114. Pugh, L. P.: Epidemic Encephalitis in Dogs, Lancet **2**:950, 1926.

115. Perdrau, J., and Pugh, L.: The Pathology of Disseminated Encephalomyelitis of the Dog (the "Nervous Form of Canine Distemper"), J. Path. & Bact. **33**:79, 1930.

metrical distribution on the two sides of the cord, as is sometimes the case in disseminated sclerosis in man, and were noted especially in the posterior columns, close to the surface. Unlike disseminated sclerosis, however, the demyelinization showed no special predilection for the walls of the ventricles.

Perdrau and Pugh concluded that demyelinization of the type common in subacute disseminated sclerosis was present in four of fourteen cases of disseminated encephalomyelitis in the dog. They suspected that the sclerotic foci mentioned by Dexler [116] in cases of encephalomyelitis in the horse may have been examples of true demyelinization. In the latter condition, however, as in cases of encephalomyelitis in dogs reported prior to the contribution of Perdrau and Pugh, most authors were concerned mainly with the inflammatory lesions, having paid no attention to possible concomitant demyelinization.

GENERAL COMMENT

The uncertainties existing in regard to the clinical and pathologic evaluation of most primary demyelinating processes of the central nervous system justify, in my opinion, an attempt at unification and classification which I have endeavored to condense in the accompanying table.

A classification which is based on the broad distinction between inflammatory and degenerative processes is difficult to establish, in view of the fact that not enough is known of the etiologic factors resulting in demyelinization. Presumably, once the etiologic factor has been determined, a possibility may be afforded to divide the demyelinating processes into degenerative and inflammatory forms. Possibility, however, does not mean certainty, as even in a condition suspected to be inflammatory, or at least infectious, in nature, histologic changes may be observed which, though grossly they appear to be inflammatory, may leave on closer histologic study considerable doubt as to their belonging to the true or to the symptomatic type of inflammatory reaction. I may recall here the example of poliomyelitis, the histologic lesions of which have been considered as typical of inflammation until the last few years, when Spielmeyer [117] expressed his belief that these changes should be considered as an expression of a symptomatic type of reaction. On the other hand, I may recall that in typical infectious diseases, such as encephalitis lethargica and measles, histologic reactions of the central

116. Dexler, H.: Beiträge zur komparativen pathologischen Anatomie der akuten Encephalitis, Monatschr. f. Neurol. u. Psychiat. **13**:97 and 210, 1903.

117. Spielmeyer, W.: Zur Histopathologie und Pathogenese der Poliomyelitis. Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:159, 1932.

I: IN MAN

A. Toxic or Infectious

1. If toxic will be designated encephalopathy, myelopathy or encephalomyelopathy
2. If infectious will be designated encephalitis, myelitis or encephalomyelitis

B. Sporadic or Familial

Sporadic cases	With patchy distribution of lesions	Acute and subacute forms	Variety of acute disseminated encephalomyelitis or acute multiple sclerosis Variety of ophthalmoneuromyelitis (Devic's disease) Variety of subacute necrotic myelitis (Foix and Alajouanine's disease) Variety of perivascular demyelinization following infectious conditions (measles, chickenpox, smallpox, vaccination, etc.) Variety of deficiency demyelinating processes (avitaminosis; pernicious anemia; Marchiafava-Bignami's disease ?)
		Chronic form	Variety of multiple sclerosis—classic type
	With diffuse distribution of lesions	Acute and subacute forms	Variety of so-called diffuse sclerosis, variously described as Schilder's disease, encephalitis periaxialis diffusa, centrolobar sclerosis, encephaloleukopathia sclerotieans, progressive degenerative subcortical encephalopathy, leukodystrophy, leuko-encephalopathia, myeloclastica primitiva, encephalomyelomalacia chronica diffusa, etc., with specification of: infantile, juvenile or adult type Variety of concentric demyelinization (Baló's disease; juvenile or adult type)
		Chronic form	Variety of diffuse sclerosis (variously described as in the acute and subacute forms), with the same specification of: infantile, juvenile or adult type
Familial cases	With patchy distribution of lesions	Chronic form	Variety of familial multiple sclerosis
	With diffuse distribution of lesions	Acute form	Variety of infantile diffuse sclerosis (Krabbe's disease)
		Chronic form	Variety of protracted infantile forms (Pelizaeus-Merzbacher's disease) Variety of juvenile cases (Scholz) Variety of cases in adults (Ferraro)

II. IN ANIMALS

Toxic or Infectious:			
Sporadic cases	With patchy distribution of lesions	Acute or chronic form	Variety of experimental deficiency demyelinating processes: avitaminosis (Gildea, Kattwinkle and Castle, and Zimmerman and Burack, etc.) Variety of experimental demyelinization due to known substances or toxic agents; potassium cyanide (Rubino), tetanus toxin (Claude and Putnam), bile (Weil and Crandall), amulsion of brain (Rivers and Schwentker) Variety of spontaneous demyelinization in animals (Schob, Scherer, Davison) Variety of disseminated encephalomyelitis in animals: nervous form of canine distemper (Pugh and Perdrau)
	With diffuse distribution of lesions	Acute or subacute form	Variety of experimental demyelinization due to known toxic or foreign agents; potassium cyanide (Ferraro)

nervous system have been described, in so-called hyperacute forms, which have been interpreted as of a toxic degenerative character (von Economo [118] and Ferraro and Scheffer [119]).

118. von Economo, C.: Die Encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung, Berlin, Urban & Schwarzenberg, 1929.

119. Ferraro, A., and Scheffer, I. H.: Toxic Encephalopathy in Measles, Arch. Neurol. & Psychiat. **27**:1209 (May) 1932.

In this connection I may also mention the variation in interpretation depending on the conception of inflammation by various investigators, cases having been reported in which one author interpreted the condition as inflammatory (Bouman's first case), though, on the basis of the same material, it was considered by another investigator as degenerative (Weimann [120]).

Nor are the histologic characteristics of an inflammatory process, as summarized by the conception of *alteratio, exudatio et proliferatio,* sufficiently well defined to justify the rigid interpretation by various investigators. Even the nature of the cells forming the perivascular exudate in inflammatory and degenerative processes is not as binding as it was once considered. While, for instance, as maintained by Lhermitte,[121] a perivascular exudate in a degenerative process never contains plasma cells, more recent investigation of experimental intoxications with various drugs and metals has proved that in certain instances, as in mushroom poisoning (Bertrand and Miyashita [122]), plasma cells are present in large numbers, even though the "perivascularitis" is related to a toxic substance.

Though a clearcut distinction between inflammatory and degenerative changes may therefore appear difficult, there is a possibility that with a better knowledge of etiologic factors one will be in a position to classify tentatively a large number of cases in the group either of the inflammatory or of the degenerative processes.

Every attempt at classification based on clinical manifestations alone is unsatisfactory. To classify a disease on the basis of clinical symptoms alone is indeed confusing. Nevertheless, this is not an uncommon effort, as evidenced by diagnoses such as ophthalmoneuromyelitis which are based dominantly on topographic localization. Classification of this form as a variety of the acute or the subacute type of demyelinating processes of the central nervous system, not differing from acute multiple sclerosis or acute encephalomyelitis, with an indication of the optic and medullary localization of the process, seems to me more justifiable and agrees also with the views recently expressed by Alajouanine, Hornet, Thurel and Rossano.[123]

To attempt a classification solely on the basis of the histologic changes would also be misleading, as, the reactions of the nerve tissue

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120. Weimann, W.: Zur Kenntnis der sogenannten "diffusen Hirnsklerose," Ztschr. f. d. ges. Neurol. u. Psychiat. **104**:411, 1926.

121. Lhermitte, J. J., in discussion of Bertrand and Miyashita,[122] p. 324.

122. Bertrand, I., and Miyashita, K.: Le problème des périvascularites toxiques, Rev. neurol. **65**:409 (Feb.) 1936.

123. Alajouanine, T.; Hornet, T.; Thurel, R., and Rossano, R.: Un cas anatomo-clinique de sclérose en plaques aiguë avec symptomatologie de neuropticomyélite, Rev. neurol. **64**:98, 1935.

to various pathogenic agents being of limited types, important errors of clinical and therapeutic evaluation might result. A grouping based, for instance, solely on the number of foci seems to me uncertain, as one focus may result from the confluence of numerous small original foci and numerous small foci present at one stage of the disease may ultimately fuse and appear as a large, single focus, depending on the stage at which death takes place. That is why the creation of a special grouping under the name "acute cervicobulbar unilocular leukopathia," as advocated by Poppi,[124] for conditions in which the focus of sclerosis appears to be single, involving the cervicobulbar region, does not seem practical.

The classification which I have attempted to present for temporary use is based on both the clinical and the pathologic characteristics of the various conditions analyzed in the preceding survey. It has the advantage of taking into account some clinical features of the disease (course, age, familial character, etc.), as well as some particularities of the pathologic process, including diffusion. It also takes indirectly into account various differences related to individual resistance and individual constitutional make-up; both of these are of necessity translated as variations either in the clinical course or in the character of some of the pathologic changes. No matter how accurate one's judgment may be in the grouping of clinical and pathologic manifestations, no definite classification is possible until more definite knowledge of the etiologic aspects of the demyelinating processes is available.

All agree that various pathogenic agents may be responsible for identical clinicopathologic manifestations. It is possible that both toxic and infectious agents may be at work, separately or concomitantly, in determining some of the best known demyelinating processes.

All have encountered cases of multiple sclerosis associated with lead poisoning. All are familiar also with the infectious theory of multiple sclerosis and with Steiner's contention that multiple sclerosis is the result of spirochetosis (Spirochaeta argentinensis). All are aware of the experimental reproduction of patchy or diffuse demyelinization after various types of exogenous intoxication.

The occurrence of diffuse sclerosis in the course of syphilis is not a novelty; Krabbe spoke of the syphilitic group of diffuse sclerosis. No reasons exist why syphilis or some other form of spirochetosis may not determine occasionally a process of patchy sclerosis.

Even though at present there is a lack of sufficient information concerning the etiology of the various forms of demyelinating processes,

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124. Poppi, U.: Contributo alla conoscenza della leuco-encefalopatie acute (leucopatia uniloculare cervico-bulbare acuta), Riv. di neurol. **7**:423, 1934.

I have endeavored in my attempt at classification to specify the known etiologic factors. It follows that the classification which I suggest is also based to a certain extent on etiologic facts.

In order to avoid confusion of clinical findings with experimental results, I have distinctly separated the observations in man from those in animals and have considered the latter from the aspects of both the spontaneous and the induced type of demyelinization.

A further large division in the classification concerns the sporadic and the familial occurrence. Though I have proposed that the familial group be classified as distinct, I have not indiscriminately designated the form as heredodegenerative. Genealogic studies related to the cases reported are too limited in number; reservation of judgment seems necessary for the present. The distinction in some of the sporadic and familial cases of infantile, juvenile and adult varieties will eliminate the necessity of considering separate clinical entities based on the factor of age in particular.

The classification of cases according to the distribution of the lesions, whether patchy or diffuse, is based on both clinical and pathologic characters, but more on the pathologic, the clinical symptoms failing at times to furnish the indication. Transitional forms will of necessity be classified in a group according to the dominance of lesions or symptoms in the case. The classification into forms with an acute, a subacute or a chronic course is essentially clinical.

The reasons for including in the classification the various individual diseases listed in the table have been separately discussed in the course of the paper.

I may add that even when the etiologic factors related to each type of demyelinization are found, classification of the process on the basis of its clinicopathologic features will still remain a necessity, even though a qualification conferred to the disease by its etiologic agent is added to the nomenclature. To illustrate this contention, I may refer to the following infectious conditions of childhood: measles, varicella, chickenpox and vaccination. In most cases the clinical course and pathologic changes are fundamentally the same, though related to a different etiologic agent. There would be no reason therefore to create as many separate clinicopathologic entities as there are infectious conditions followed by the same neurologic complication. This is in view of the fact that after certain infectious conditions of adulthood, as mentioned in the body of the paper, the same histopathologic process may result. If a classification based only on the etiologic factor were accepted, one would have to resort to naming as many varieties of encephalitis as one may know pathogenic agents capable of producing that condition.

It would be more simple to group all the encephalitides or encephalopathies following infectious diseases which are characterized by the same fundamental aspect of perivascular demyelinization under the one heading of varieties of encephalitis following acute infectious conditions (measles, varicella, vaccinia, etc.), as provided in the table. This would save repetition and confusion.

The finding of the etiologic factors may not of necessity result, therefore, in drastic changes in the classification which I present but will undoubtedly contribute to clarification, by the final addition of the qualification of the etiologic agent.

With respect to the various supposedly clinicopathologic entities which I have analyzed (Krabbe's disease, Baló's disease, Pelizaeus-Merzbacher's disease, ophthalmoneuromyelitis, subacute necrotic myelitis, etc.), I believe that their inclusion in the group of demyelinating processes, not as entities but as clinical varieties possessing certain clinicopathologic characteristics, will be of assistance to the clinician. It will relieve him from thinking in terms of pure clinical facts and confusing clinical entities—a circumstance carrying with it artificial responsibilities of diagnosis. It will enable him to make use also of a pathologic approach in considering the case as a demyelinating condition to be classified grossly according to a broader conception, free from the limitations of definite clinical entities.

SUMMARY AND CONCLUSIONS

In using the nomenclature proposed in the accompanying table for the designation of the various types of demyelinating processes of the central nervous system, one will find that it is necessary to use a rather long title for the condition for which it is intended. I believe, however, that this inconvenience will be counterbalanced by the clarification which will result from its use and by the advantage of eliminating the confusing designation of the disease by an author's name. This last advantage is particularly important in the cases of the demyelinating processes of the central nervous system in which numerous conditions fundamentally identical have been variously described under the names of various persons.

To denominate the process I therefore recommend, first, the use of the word "encephalomyelopathy" or "encephalomyelitis," according to the clinician's conception of the particular clinical case under discussion. The second recommendation is the additional qualification of the sporadic or the familial occurrence, the denomination reading, therefore, at this point; encephalomyelitis, a sporadic or a familial case. The specification of the acute, subacute or chronic course may now be added, with the additional qualification of demyelinization. Then the clinician's con-

ception of the patchy or the diffuse distribution of the lesions should be inserted, the full title at this point reading: encephalomyelitis, a sporadic case of an acute (or a subacute) form of demyelinization with patchy (or diffuse) distribution of the lesions. The final suggestion is the addition to the title of the actual nomenclature of the disease, which would stand as a variety of the general process. A full title for a disease would therefore read as follows: encephalomyelitis, a sporadic (or familial) case of an acute (or a subacute) form of demyelinization with patchy (or diffuse) distribution of the lesions; variety of ophthalmoneuromyelitis (or acute multiple sclerosis).

If for a more concrete example one wishes to indicate the so-called classic type of multiple sclerosis, the following designation should be used: Encephalomyelitis, sporadic case of the chronic form of demyelinization with patchy distribution of lesions; variety of multiple sclerosis. If, on the other hand, one wishes to designate a case of the so-called Pelizaeus-Merzbacher disease, the full title of the condition should be: encephalomyelitis, familial case of the chronic form of demyelinization with diffuse distribution of lesions; variety of the protracted infantile type.

In the event of death pathologic investigation of the lesions will, within the limits of possibilities, determine more accurately the inflammatory or the degenerative nature of the original process and stamp more definitely the disease as encephalomyelitis or encephalomyelopathy.

For the practical purposes of nomenclature in the wards or the daily discussion of clinical cases, a shorter designation of the process is suggested. The disease should be named as an acute or a chronic demyelinating process, with the addition of the special variety applying in the case. In the case, for instance, of so-called ophthalmoneuromyelitis, the denomination might be worded: acute (or subacute) form of demyelinization, variety of ophthalmoneuromyelitis. In the case of so-called Schilder's disease, the denomination might read: acute (or subacute) form of demyelinization, variety of diffuse sclerosis; infantile, juvenile or adult type.

DISCUSSION

DR. J. J. PUTNAM, Boston: The classification of the demyelinating diseases of the white matter is, in my opinion, the most confusing problem in neurology—not even excepting the neuritides. Conditions belonging to this great class all have certain similarities, and yet they are divisible into groups—one might almost say into as many groups as one wishes to make. How should one go about classifying them? Should one try to make as many or as few groups as possible?

It seems to me that before deciding this question it is necessary to determine what one hopes to gain by a classification. Is it precision in clinical diagnosis? If that is the case, presumably one should try to classify demyelinating processes into as many categories as possible. Or does one hope to make progress in sorting out the mechanism and the cause of the various groups of diseases? If that is the case,

one would probably do well to try to recognize as many similarities as possible between different groups, since almost nothing is known of the etiology of any of them. I think that there is a distinct disadvantage in making too many subgroups in studying the pathologic processes in these diseases. For example, in such a well defined group as multiple sclerosis each condition has its own individuality and physiognomy. I agree with Dr. Ferraro that the dividing line between multiple sclerosis and diffuse sclerosis is extraordinarily hard to draw and that it is often purely an arbitrary matter whether a condition is classified as one or as another. The same may be said of the attempt to distinguish cases of acute multiple sclerosis from those of encephalomyelitis.

I believe that there is a temperamental difference among neuropathologists in this respect. Some prefer to divide diseases into small categories, while others like to group them all together. It may be taken as a sign of greatness to recognize one's own bias, as did the late Professor Spielmeyer in his remarkable paper *"Infektion und Nervensystem."* He stated that this class of diseases should be divided as closely as possible but admitted his inability to make a differential diagnosis between the histologic reactions that he observed in different diseases of this class. He wrote: "What is the process in multiple sclerosis, for example? I myself have considered multiple sclerosis to be of inflammatory origin for many years, but if somebody should say that the infiltration is only a symptomatic inflammation as a result of destruction and reparation, I should not be able to contradict him." Spielmeyer's whole paper might be read as a plea for just such a review as is this study by Dr. Ferraro.

The same principle applies to all the divisions that have been erected between the various groups of demyelinating diseases. They do overlap, it seems to me, to a great extent. The etiology as known at present helps one, on the whole, extremely little. Indeed, I am not sure that it does not make matters worse. As far as combined system disease is concerned, the classification is satisfactory, to be sure, but when one considers some of the acute disseminated lesions, the matter is extraordinarily difficult. I believe that in many instances it is impossible to tell whether one is looking at the lesion produced by acute postvaccinal encephalitis, trauma to the brain, such as was demonstrated by Dr. Schaller yesterday, or nitrous oxide poisoning. Some specimens from cases of these various diseases are almost indistinguishable. I challenge anybody to tell which is which without further knowledge of the case.

I believe that one great difficulty in studying these diseases results from the use of the term "inflammatory" and "encephalomyelitis," just as the term "neuritis" has been a stumbling-block in studying the neuritides. I recommend, however, a procedure that is exactly the opposite of what Dr. Wechsler suggested in regard to the neuritides, namely, that one should keep the name "encephalomyelitis" for the whole class, just as the name "arthritis" is used to designate almost any involvement of a joint. If this is done, however, I believe that one should carefully school oneself to take the designation in as broad a sense as possible and not to leap at once to the conclusion, as I think one is all too likely to do, that "itis" means infection. It does not in arthritis, and it does not in many current usages. While one could turn to encephalomyelopathy for a generic term for the group of diseases under consideration, I think that there would be disadvantages. One might possibly exclude some infectious disorders because of inability to recognize them—and many such disorders are at present recorded in the "Quarterly Cumulative Index Medicus" as encephalomyelitis—and one would take a long step backward if one did not utilize the conditions already classified. It could then be left for future observers

to decide which, if any, of the disorders are of infectious origin. I believe that one should assume that none of them is until at least one or two of Koch's postulates have been fulfilled. So far as I am aware, this has not been done for any disease in this case.

I should appreciate hearing Dr. Ferraro's point of view on inflammation in regard to this class of diseases, and I wish to compliment him on his work, to which a ten minutes' discussion cannot do justice. He has compiled a complete, extremely useful, interesting and valuable series of observations on these obscure diseases, of which no one observes many cases at a time. This study should be a help and guide in further investigations as to the etiology and clinical diagnosis of primary demyelinating processes of the central nervous system.

Dr. I. S. Wechsler, New York: I too wish to compliment Dr. Ferraro on the boldness of the attempt to tackle a problem which in the present state of knowledge, I believe, cannot be unified. He tries to make a new classification, and in some way a simplification, but I wonder if he has not really complicated matters. There is a grave abuse of eponyms in neurology. It is customary to attach the name of an original observer to a certain disease, but if this tendency is multiplied indefinitely, there will be names and nothing else. One man observes a neurologic condition or two and describes a special pathologic condition, and the condition is regarded as a new clinical entity. Certainly, the disorder is not always new.

Dr. Ferraro mentioned Pelizaeus-Merzbacher's disease. I wonder how many of the members present have ever observed a case of that condition. It is doubtful whether any one has really observed one in the past generation, and yet neurologists go on talking about Pelizaeus-Merzbacher's disease.

Similarly, one describes two or three conditions with a slightly different manifestation, for instance, demyelinization running in an arc or a circle instead of, perpendicularly, and calls it a new disease. If one thing is known, it is that the reaction of the nervous system is dependent not so much on what attacks it as on the nervous system itself. The nervous system reacts in a peculiar way to certain noxious agents, and in order to know what actually happens, not only the various agents but the nature of the nervous system itself must be studied. Therefore, any unification on the basis either of clinical study—which is often misleading—or of pathologic changes—which are as yet confusing—is not satisfactory. If neurologists would bide their time and wait until the etiologic factors of diseases were known, there would be a better opportunity for classifying them.

As regards multiple sclerosis, for instance: It is said to be a classic disease, a typical disease. The only classic or typical feature about multiple sclerosis is that it is never typical or classic and that in all cases the manifestations are atypical. If one indulges in a little armchair thinking about multiple sclerosis, a number of observations can be made: (1) It is a disease of comparative youth; (2) it is paroxysmal or spasmodic; that is, it comes and goes and gets better and worse for no known reason, and (3) it occurs among certain peoples. It is infinitely more common in northern countries, such as the Scandinavian countries, Great Britain, Northern Germany, Poland and Russia, than in the United States. It is strange that in spite of the fact that the population of the United States is preponderantly derived from northern countries—British, Irish, Scotch, German and Scandinavian—the incidence of multiple sclerosis in this country, even among persons of these nationalities is infinitely smaller than it is among the same persons in their own countries. I once saw a map of Great Britain in which certain counties were dotted black to indicate the large number of cases of multiple sclerosis; in adjoining counties there were few cases of the disease. Whether diet has anything to do with

the problem, whether the disorder is due to a virus, whether it is a toxic condition or whether lead has anything to do with it is an open question. It may be that one is dealing with not one disease, not with one syndrome, but a congeries of syndromes, and it is possible that the pathologic substratum is the only thing about multiple sclerosis that is unified. That is why I believe that, although clinical study is valuable in itself, it is hardly likely to give the final answer. When I see a study of multiple sclerosis which indicates that 72 per cent of the patients show a Babinski sign, 14.5 per cent nystagmus to the right and 19.25 per cent nystagmus to the left, I wonder what is the meaning of such studies.

I do not wish to discourage clinical studies, but it seems to me that only when it is realized that etiologic facts and the relation of the nervous system to etiology are more important than clinical manifestations will something about the various diseases be learned. Nonetheless, I think that Dr. Ferraro has taken a step in the right direction. Any unification, any simplification, is wise, even though it is only tentative.

DR. J. H. GLOBUS, New York: Classification of disease is a useful method of cataloging the clinical and pathologic manifestations of the disease process. It is useful particularly when little is known of the causative factors.

It is doubtful, however, whether Dr. Ferraro has given a classification more workable than that which has existed up to the present. Personally, I believe it is a little too involved. With but few exceptions the present classification is quite useful. One might refrain from assigning a place for Pelizaeus-Merzbacher's disease, of which there have been few cases, or for another obscure demyelinating process, of which there are one or two examples. I do not, however, wish to be understood to say that efforts at classifying disease should be discouraged.

Another question was brought up in the discussion: Should such a term as encephalopathy or neuropathy be introduced? I think that these terms are exceedingly useful, particularly if one accepts the view that it is necessary to distinguish inflammatory from degenerative disease. This distinction is old and extremely useful. I believe it is now fully realized that there may be, on one hand, a pathologic process in the brain and elsewhere which is inflammatory and, on the other hand, pathologic changes which are essentially degenerative. When I say inflammatory I mean a pathologic process induced by an intrinsic living agent. When the disease is produced by an agent causing a primary dissolution of tissue, whether it takes the form of demyelinization, swelling of the axis-cylinders or swelling of some of the cell elements, it may be regarded as degenerative. Once the nature of the pathologic process is identified, the cause is more easly recognized.

DR. F. WERTHAM, New York: I think that Dr. Ferraro has done a fine thing in drawing attention to the great complication of nomenclature in cases of diffuse sclerosis. Those of the members who attended the International Congress in Bern, Switzerland, may remember that Professor Marburg spoke about that subject. In some respects Dr. Ferraro has been too modest. He has failed to include his own work, his experimental histopathologic investigations. By injecting certain toxins he has produced diffuse demyelinization in cats and, if I remember correctly, in monkeys. Some of his preparations look exactly like specimens of diffuse sclerosis in man. They look much like other conditions, too. For example, in monkeys I have seen what seemed to be subacute combined degeneration in the spinal cord, and in a number of monkeys there are diffuse processes of this demyelinization in the brain. This work of Dr. Ferraro and the occurrence of the changes in animals may give a clue to the solution of this problem.

Dr. Ferraro himself and some of the discussers have repeatedly used the word "confusing," saying that this is a "confusing" subject. When something is "confusing," there must be something wrong with the theories. Why should diseases which have been studied, why should the subject in general, be "confusing"? It is not confusing; it is merely complicated. What *is* confusing are the time-honored theories about these conditions.

It seems to me that the disease is *not* due to a special agent, a toxin which reaches the central nervous system and makes it react in any specific manner described in textbooks. In many different conditions the reaction is the same. The best example of that is demyelinization. Dr. Tracy Putnam has done some excellent work in pointing out that focal demyelinization is about the same in what must be considered different kinds of clinical conditions. As I say, Dr. Ferraro pointed out in his own work that he can produce by a subcutaneous injection of toxin a lesion that looks exactly like a typical diffuse demyelinization, although the process is associated with a different disease.

Confusion has always risen from the fact that one expects the peculiarity of a disease to express itself in the form and in the quality of the lesion itself. In reality it does not. The different kinds of focal and diffuse lesions are remarkably alike. I found that out in a study of dementia paralytica, diffuse sclerosis and disseminated sclerosis, in which I observed small focal lesions with no specific distinction. I remember showing specimens to Professor Spielmeyer. It was impossible to tell what the disease was.

One thing that has been emphasized in this discussion is the question of names. It seems to me that if one places so much importance on names, either condemning or commending them, there will gradually result a scholastic debate about nominalism. Emphasis will be placed on an abstract philosophic question, and the actual symptoms and the things with which neurologists deal will be lost sight of. It seems to me that the old neuropathology—and in my opinion the old neuropathology reaches well into 1936—is far too formalistic and ascribes specific causes to specific processes in the brain. Hence the preoccupation with the names of diseases and with isolated histologic details. Kant wrote a "Critique of Pure Reason." If neurologists go on like this, they will be waiting for some one to write a "critique of pure neuropathology."

I think that the positive aspect is simple. If the brain is regarded as an organ like any other, why cannot one describe the disease and the different kinds of phenomena associated with it? Why cannot one in the study of the diseases under consideration pay attention not to the etiology alone, because it is neither the etiology nor the lesion alone that tells the story, but to the symptoms and processes that lie between these two? If one combines the study of all these questions with the study of the rest of the body, one finally arrives at certain typical empirical observations which can be made in either clinical experiments or experiments with animals, and there is no need to lose one's self in this problem of classification and to speak of "confusion" when looking for a specificity which does not exist in the brain.

Dr. A. Ferraro, New York: Dr. Wechsler has asked, "Why classify?" My answer is that classification in this special group of diseases is intended for simplification. I believe that the use of the term "primary demyelinating processes" is not only an improvement but a clarification of the terms: acute encephalomyelitis, ophthalmoneuromyelitis, acute multiple sclerosis, Schilder's disease, Krabbe's disease, Baló's disease, etc. I believe that the use of the general terminology of demyelinating processes and of the descriptive terms acute or chronic form and

patchy or diffuse distribution of lesions simplifies matters. If Dr. Wechsler is satisfied with the names as they are, he should also be willing to accept the conception that the diseases under consideration constitute definite clinicopathologic entities. In that case I should like to know on what criteria a clinician should base a diagnosis in a case of encephalomyelitis as against one of ophthalmoneuromyelitis, of acute multiple sclerosis or of the so-called typical multiple sclerosis. I believe that clinical knowledge as well as knowledge of histology does not allow one to make a differential diagnosis in the various forms of demyelinating processes with patchy or diffuse distribution of lesions. The fact is that a case presented at a conference of neurologists—this has occurred in real experience—has been variously labeled as one of acute encephalomyelitis, acute multiple sclerosis, ophthalmoneuromyelitis, typical multiple sclerosis, etc., according to the subjective feeling of the various discussers.

Dr. Globus seems to be in favor of simplification in the sense of dividing at least the demyelinating processes into two large categories, the inflammatory and the degenerative, and of labeling the first encephalitis or encephalomyelitis and the second encephalopathy or encephalomyelopathy. This is entirely desirable, and I agree with him. But in practice what name will be applied to a case of encephalitis and what to one of encephalopathy? Certainly, from a clinical standpoint one often lacks leads to determine whether a process should be considered inflammatory or degenerative. From the standpoint of pathology, instances are known in which the same type of disease, i. e., ophthalmoneuromyelitis or Schilder's disease, has been described by some authors as an inflammatory and by others as a degenerative condition. There are also cases of diffuse sclerosis in which after a study of the pathologic material the reaction has been considered inflammatory by one investigator and degenerative by another, though the decision was based on the study of the same slides.

This would not be surprising, as I asked: Does one really know where degeneration ends and where inflammation begins? I doubt whether progress has really been made in the last twenty years, and I am more preplexed about the subject now than I ever was before. There are even reports of experiments in which injection of toxic substances in animals has been followed by a reaction of the central nervous system which was inflammatory. If I withheld from a pathologist the knowledge of the agent which had been used in producing certain lesions and asked him whether the condition was produced by a degenerative or by an inflammatory agent, I am fairly sure that he would not always be able to answer the question. I believe, therefore, that for the present I should leave to the clinician or to the pathologist the liberty of choosing in the classification of the demyelinating processes the name "encephalomyelopathy" or "encephalomyelitis." If he believes that he is dealing with an inflammatory process, he will call the condition encephalomyelitis; if he believes that he is dealing with a degenerative process, he will call it encephalomyelopathy.

But irrespective of whether the process is inflammatory or degenerative, I believe that to substitute for the various names by which the same fundamental condition of demyelinization is at present known a general term indicating a demyelinating process with patchy or diffuse distribution of lesions, of acute or chronic and sporadic or familial type, is definitely a simplification and clarification.

Dr. J. H. Globus, New York: I think that a vital question has been raised. I should like to question some of the statements made by Dr. Ferraro. The majority of the members are not pathologists. They may be misled by statements such as were made, namely, that the presence of infiltration is sufficient to identify inflammation. At the same time that they are given a simplified classification to which

they will be held rigidly, they are given free choice to decide according to their own likes and dislikes whether the disease is inflammatory or degenerative. I believe that some day this problem of distinguishing between these two pathologic processes should be made a part of a symposium, so that it could be freely discussed. Those who are asked to decide on clinical evidence alone whether they are dealing with an inflammatory or a degenerative process should be fully informed as to what is meant by degeneration and what by inflammation. This is important because this distinction is the crux of many of the present problems in searching for the etiologic factors responsible for some obscure but prevalent diseases of the central nervous system.

Dr. A. Ferraro, New York: I still maintain that there are cases in which histologically one cannot differentiate between an inflammatory and a degenerative condition. The fundamental course of inflammation is represented not only by the presence of perivascular exudate. Perivascularitis alone, I agree with Dr. Globus, does not constitute inflammation, but when the three fundamental characters of proliferation, degeneration and exudation are present, one is authorized in speaking of an inflammatory process. There are, however, undoubtedly purely degenerative processes in which the triad—exudation, proliferation and degeneration—is present, and I do not know of any certain method of differentiating the histologic picture from that of a typical inflammatory condition. The concept of symptomatic inflammation has so complicated matters that I agree with Dr. Globus that this whole subject should form the object of a symposium in which debate might be more detailed.

Case Reports

CHRONIC BILATERAL SUBDURAL HEMATOMA

Encephalographic Diagnosis, with Report of Three Cases

WILLIAM L. HOLT JR., M.D., AND GROSVENOR B. PEARSON, M.D., BOSTON

Encephalographic findings in cases of unilateral subdural hematoma have been reported by several authors.[1] Abbott [2] and Naffziger and Brown [3] have independently mentioned the use of encephalography in a case of bilateral hematoma. We encountered three cases of this condition in as many months and could find no report of a series of cases of bilateral subdural hematoma in which there were encephalographic findings. That the patients in our series came to a hospital for psychopathic patients though excellent neurosurgical clinics were easily available is not surprising when one recalls that Virchow's original description of the pathologic structure in this condition was based on autopsy material obtained from patients with alcoholism and mental diseases. The considerable incidence of unsuspected subdural hematoma among patients with mental disease in the Massachusetts state hospitals has recently been described by Allen, Daly and Moore.[4] We here present reports of the three cases which we observed, with the encephalographic findings which led to diagnosis and surgical relief.

From the Boston Psychopathic Hospital; Dr. C. Macfie Campbell, Director.

Read by title at the Sixty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 3, 1936.

1. Dereux, J., and Hayem, A.: Hématome sous-dural chronique posttraumatique: Aspect radiographique, Rev. neurol. **2**:839-843, 1933. Dickerson, D. G.: Intracranial Hemorrhage, Northwest Med. **28**:535-543, 1929. Frazier, C. H.: Surgical Management of Chronic Subdural Hematoma, Ann. Surg. **101**:671-689, 1935. Lindemulder, F. G.: Subdural Hematoma Shown by Encephalography, Am. J. Roentgenol. **25**:512-514 (April) 1931. Lippens, Adrien, and Dejardin, Leo: La valeur de l'encéphalographie dans le diagnostic, le pronostic, et l'évaluation des reliquats des traumatismes cranio-cérébraux, Presse méd. **42**:455-457, 1934. Madigan, Patrick Sarsfield: Encephalography in Cerebral Surgery and Report of a Case of Pachymeningitis Interna with Cyst Formation Successfully Removed, Mil. Surgeon **66**:390-397, 1930. Nash, C. C.: Chronic Subdural Hematoma, South. M. J. **28**:779-785, 1935.

2. Abbott, W. D.: Value of Encephalography as Diagnostic and Therapeutic Agent, Radiology **23**:672-676 (Dec.) 1934.

3. Naffziger, H. C., and Brown, H. A.: Chronic Subdural Hematoma in Infants, S. Clin. North America **14**:1465-1483, 1934.

4. Allen, A. M.; Daly, B. B., and Moore, M.: Subdural Hemorrhage in Psychotic Patients: A Study of Two Hundred and Forty-Five Cases Found Among Three Thousand One Hundred Consecutive Autopsies, J. Nerv. & Ment. Dis. **82**:193-196, 1935.

REPORT OF CASES

CASE 1.—*History.*—H. T., a white man aged 48, was admitted to the Boston Psychopathic Hospital on Dec. 9, 1935, because he had been acting in a confused manner. He had worked as a farm laborer and enjoyed excellent health until Dec. 1, 1935, when he fell from a hay-loft. He was unconscious for a few minutes, according to his own statement, no one having witnessed the accident. He complained thereafter of pain in the face and head and often held his hands over both temporal regions to relieve the pain. On December 5 he felt ill, and on the following night he tore up his bedding and wandered out of the house. On December 7 he thought he had had a shock, fell to the floor and cried out as though in great pain. A physician was called for the first time. Involuntary movements of the extremities were observed, but because of marked mental confusion the patient was sent to a hospital for psychopathic patients.

Examination.—Except for a few fibrillary twitchings of the muscles of the calf and a blood pressure of 150 systolic and 100 diastolic, the results of examination were not remarkable. Ophthalmoscopic examination revealed no abnormality. The patient could offer no explanation of why he fell and gave widely contradictory dates for the event. He was affable and poorly oriented and had a marked defect of memory. The mental picture was recognized to be symptomatic of trauma to the head or vascular accident. Because of the history, the possibility of subdural hematoma was considered. Lumbar puncture on Dec. 12, 1935, yielded normal findings, including a negative Wassermann reaction. No sign of increasing intracranial pressure or localizing symptom was found until December 17, when there occurred a generalized convulsion lasting five minutes, followed by a rhythmic tremor of the left arm and hand. Dr. Harry Solomon, who saw the patient on the following day, noted slight weakness of the left side of the face and tremor of the left hand; he advised encephalography to aid in localizing the lesion.

First Encephalogram (fig. 1).—On December 19, 260 cc. of cerebrospinal fluid was replaced with sufficient oxygen to bring the final pressure with the patient sitting to 150 mm. of water. This procedure was carried out with the von Storch[5] apparatus for displacing fluid with gas in a closed system, with the patient under anesthesia induced with the intravenous injection of 7 grains (353 mg.) of pentobarbital sodium. Bilateral subdural cysts were made clearly visible by gas outlining the limiting membrane well above the underlying cortex.

Operation.—On December 23 Dr. James L. Poppen made bilateral occipitoparietal trephine openings. Immediately below the dura he encountered cysts, from each of which escaped about 30 cc. of a thick golden-yellow fluid. The cavities were apparently of about equal size. The total protein content of the fluid obtained from the right side was 2,811 mg. per hundred cubic centimeters and of that from the left 3,186 mg. The ventricles were then tapped, and 15 cc. of clear fluid was obtained, which was normal on examination. The ventriculogram made immediately after the operation confirmed the encephalographic finding of ventricles of normal size.

Second Encephalogram.—On Jan. 28, 1936, encephalography was repeated, 200 cc. of fluid being replaced with oxygen. The ventricles were somewhat larger, and much less gas was present above the cerebral hemispheres.

Course.—As convalescence was protracted, the patient was transferred to another state hospial, where osteomyelitis of the right middle finger developed on

5. von Storch, T. J. C.: Spinal Fluid Dynamics During Encephalography, New England J. Med. **211**:773-774, 1934.

March 26, requiring amputation. Auricular fibrillation developed, and the patient died a few days later, April 12, 1936. Permission for postmortem examination was refused. The mental condition showed no marked improvement during the whole period of hospitalization.

CASE 2.—H. W., a white man aged 43, was admitted to the Boston Psychopathic Hospital on Dec. 1, 1935, because he had left home after writing notes in which he threatened suicide. He was an employee of a street-car company and had been heavily addicted to the use of alcohol. He had been well until June 1931, when he was struck by an automobile. He was semiconscious when picked up. He was again struck on the head in September 1934 and was unconscious for five hours. An extensive scalp wound required suturing at the Boston City Hospital, which he left against advice three days later. After the second injury he had frequent headaches, lost interest, became depressed, drank more heavily and got into debt. After losing his home and then his job, he planned to commit suicide but was apprehended by the police.

Fig. 1 (case 1).—First encephalogram.

Examination.—There were: slightly impaired vision, poor reaction of the pupils to light and in accommodation, unsteady gait, tremors of the tongue and fingers, some weakness of the left side of the face, exaggerated tendon reflexes and normal fundi. The breath was alcoholic. Lumbar puncture on Dec. 4, 1935, revealed normal findings, including a negative Wassermann reaction. The patient was slow in action and speech and said he felt depressed and anxious. Memory and judgment were impaired. Because of the history of change in personality following the second injury to the head an encephalogram was made.

First Encephalogram.—On Dec. 10, 1935, 280 cc. of cerebrospinal fluid was replaced with oxygen (fig. 2 *A*). The anteroposterior view showed a large subdural collection of gas over the right hemisphere and a smaller amount over the left. The ventricles were well filled, the right being slightly smaller; both were displaced toward the left.

Following this procedure the patient quickly regained a feeling of well-being.

Operation.—On Dec. 23, 1935, Dr. Poppen made two symmetrically placed bur holes in the skull; two cysts were encountered beneath the dura. About 30 cc. of

golden yellow fluid was obtained from each side, the cystic cavities being apparently of equal size. The fluid obtained from the cysts was grossly similar to that obtained in case 1.

Second Encephalogram.—On Feb. 5, 1936, 230 cc. of fluid was replaced with oxygen (fig. 2*B*). The ventricles showed a marked increase in size. The absence of gas over the hemispheres was striking.

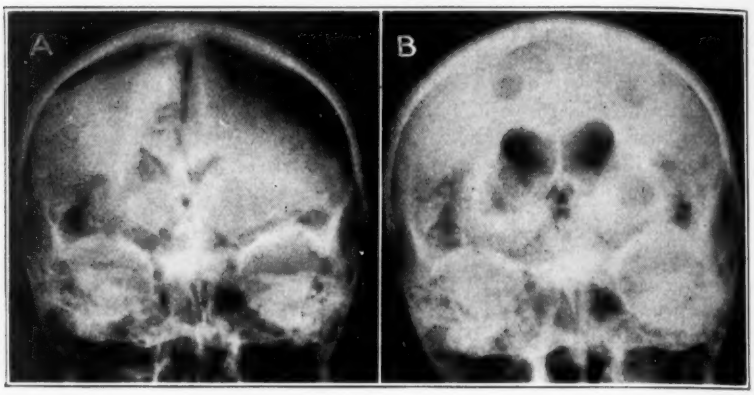

Fig. 2 (case 2).—(*A*) First encephalogram and (*B*) second encephalogram.

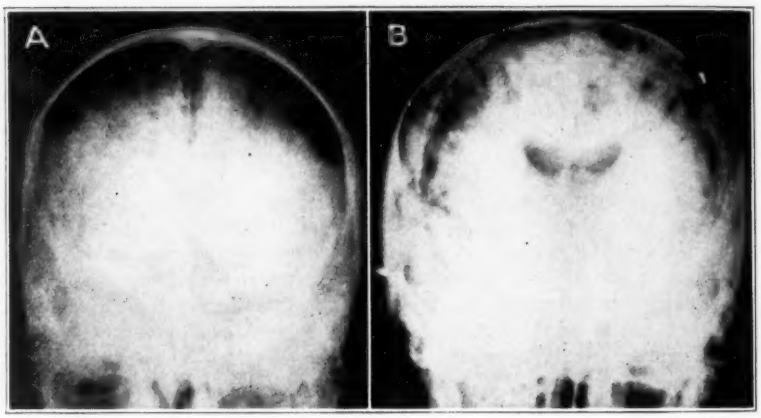

Fig. 3 (case 3).—(*A*) First encephalogram and (*B*) second encephalogram.

Course.—The patient was discharged on Feb. 22, 1936, as recovered. Three months later he was back at work, feeling entirely well.

CASE 3.—W. E. H., a white man aged 48, an insurance salesman, was admitted to the Boston Psychopathic Hospital on March 11, 1936, because of convulsive seizures since birth and episodic misappropriation of funds during a period of twenty years. His seizures were attributed to an injury at birth, for there had been a difficult forceps delivery and cyanosis, followed by a convulsion at the age

of 5 days. Minor convulsions occurred at irregular intervals until the age of 17 years, when attacks of grand mal supervened. The latter were often preceded by headache on the right side.

Examination.—At the time of admission mental, physical and neurologic examinations revealed no significant abnormality. Because of the seizures, Dr. Harry Solomon suggested that an encephalogram be made.

First Encephalogram.—On March 20, 1936, 140 cc. of cerebrospinal fluid was replaced with oxygen, no attempt being made to drain off all the available fluid. Large symmetrical collections of gas were present over both cerebral hemispheres (fig. 3 *A*). This gas appeared to be in the subdural space, entirely outside the arachnoid. No cortical sulci were rendered visible, nor were the ventricles seen. The after-care of this patient was modified by the use of Schwab's [6] oxygen inhalation apparatus to shorten the period of acute discomfort by hastening the absorption of the injected gas. The encephalographic findings were thought to warrant bilateral trephination.

Operation.—On March 26, 1936, Dr. Gilbert Horrax made two parieto-occipital bur holes in the skull. Immediately beneath the dura on each side was a large subdural cyst, from which about 50 cc. of clear fluid escaped. The total protein content of each fluid was about 1,100 mg. per hundred cubic centimeters. The cyst on the right side appeared to be considerably larger than that on the left.

Second Encephalogram.—On April 27, 1936, 182 cc. of fluid was replaced with oxygen. Large, nearly symmetrical ventricles were found, together with fairly evenly distributed small collections of gas in the subarachnoid space over the hemispheres (fig. 3 *B*).

Course.—After the second encephalogram the patient had girdle pains for a few days and then a normal convalescence. He was discharged as recovered on May 14, 1936.

COMMENT

In the three cases reported the condition is believed to belong to the group of liquid subdural hematomas described by Munro and Merritt [7] and Naffziger.[8] In the second and third cases the lesion was certainly old, and, as suggested by Zollinger and Gross,[9] the cysts may represent an advanced stage of progressive dilution and enlargement of a hematoma which was originally small. It is probable that the blood was from the first mixed with a considerable amount of cerebrospinal fluid. Encephalography after operation showed enlargement of the ventricles, presumably representing passive dilatation secondary

6. Schwab, R. S.; Fine, Jacob, and Mixter, W. J.: The Reduction of Post-encephalographic Symptoms by the Inhalation of 95 Per Cent Oxygen, Arch. Neurol. & Psychiat., to be published.

7. Munro, Donald, and Merritt, H. Houston: Surgical Pathology of Subdural Hematoma Based on a Study of One Hundred and Five Cases, Arch. Neurol. & Psychiat. **35**:64-78 (Jan.) 1936.

8. Naffziger, H. C.: Subdural Fluid Accumulations Following Head Injury, J. A. M. A. **82**:1751-1752 (May 31) 1924.

9. Zollinger, R., and Gross, R. E.: Traumatic Subdural Hematoma: An Explanation of the Late Onset of Pressure Symptoms, J. A. M. A. **103**:245-249 (July 28) 1934.

to removal of fluid from a cyst. As reported by Friedman,[10] increase in the size of the ventricles after injury to the head takes months to appear. In our cases the increase in size was evident after a few weeks.

The subdural collections of gas over the hemispheres in case 3 were similar to those observed by Cramer [11] and other workers and were considered by them to be due to faulty technic in injection of air or possibly to indicate marked cerebral atrophy. The advice to the surgeon to trephine in case 3 was based partly on curiosity and partly on experience in the two preceding cases. Fortunately, the observations at operation justified the procedure, and they suggest that the neurosurgeon should trephine in cases in which the encephalographic findings are similar. In some instances operation will be disappointing, for a subdural collection of gas does not necessarily indicate a subdural hematoma. Leary [12] reported a group of cases in which there was subdural neomembrane over the cerebral hemispheres, the cavity of the cyst being obliterated, owing apparently to spontaneous absorption of the hematoma. This possibility may explain why Fränkel and Koschewnikow [13] observed only thickened membranes at operation after an encephalogram had shown large subdural collections of air.

How does gas enter the subdural space? In cases 1 and 2 we believe that the gas escaped from the subarachnoid space through small tears. Howard [14] suggested that tears may occur at the site of pacchionian granulations and are due to rough manipulation of the head when the brain is no longer cushioned by fluid. In case 3 the gas was probably subdural in its ascent from the site of injection, as in this case neither the sulci nor the ventricles were filled. This is the explanation offered by Pendergrass,[15] who reported on similar encephalograms. In many encephalograms it is not possible to distinguish the presence of subdural gas alone from that of both gas and encysted fluid over the same general region. Only in case 1 was the wall of the subdural cyst visible and distinct from the surrounding gas.

CONCLUSION

Three cases are reported in which encephalographic findings and observations at operation were characteristic of chronic bilateral subdural hematoma.

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10. Friedman, E. D.: Head Injuries: Effects and Their Appraisal; III. Encephalographic Observations, Arch. Neurol. & Psychiat. **27**:791-810 (April) 1932.

11. Cramer, F.: Occurrence and Significance of Air in Subdural Space After Encephalography, Bull. Neurol. Inst. New York **3**:506-512, 1934.

12. Leary, Timothy: Subdural Hemorrhages, J. A. M. A. **103**:897-903 (Sept. 22) 1934.

13. Fränkel, S. R., and Koschewnikow, A. M.: Die Encephalographie bei Psychischen- und Nervenkrankheiten des Kinde- und Säuglingsalters, Acta radiol. **14**:349-373, 1933.

14. Howard, C.: Observations on Encephalography, Am. J. Roentgenol. **32**: 301-310, 1934.

15. Pendergrass, E. P.: Encephalography: Explanation of Possible Error in Technique, Am. J. Roentgenol. **25**:754-757 (June) 1931.

In case 1 an encephalogram showed the wall of the subdural cyst outlined by the gas, a finding considered by us to be pathognomonic.

In case 2 an encephalogram showed small ventricles, filling of the sulci and large collections of gas over the hemispheres, findings which we considered to suggest the presence of bilateral subdural hematoma.

When the ventricles are displaced from the site of the larger collection of gas the larger subdural cyst is probably, but not necessarily, on the side of the larger accumulation of gas.

When large subdural collections of gas are seen over both hemispheres but the ventricles are not visible no reliable encephalographic interpretation can be made, but subdural hematoma may be present. In the presence of a history of injury to the head bilateral trephining is indicated.

Obituaries

FRANCIS RHODES FRY, M.D.
1853–1937

Francis Rhodes Fry, of St. Louis, who died on Jan. 25, 1937, was born in Cincinnati, Oct. 1, 1853. In 1880 he began to practice medicine. For fifty years he was actively in practice, keeping up his interest in medicine in his chosen field of neurology and psychiatry until struck down by a coronary thrombosis, while examining a patient in his office. This summarizes the story of an unusual man, whose active career and span of medical work are worthy of notice. As a physician, he saw and felt the great discoveries and the drives and trends of the modern conception of disease. He saw laid the foundations of the specialties of neurology and psychiatry and in his way became a part of that development. A life lived actively and receptively toward the changes and revaluations of medicine, and particularly of nervous and mental diseases, is in need of a more detailed study than is possible here. That it cannot be done lies within the personal characteristics of Frank Fry himself. He was a reticent, somewhat inarticulate man —modest, shy and retiring. He has left little of a documentary nature on which a biographer might depend for his data. What he thought of things, how he reacted to the changing moods of the time he lived through are matters that can be only speculated about—not known. He was a physician much respected and looked up to by friends and colleagues. His patients, throughout his long professional life, loved him and clung to him persistently, in spite of new methods and various models of neuropsychiatry, as they appeared in St. Louis. Even when the physical burden of his age made Frank Fry move slowly and guardedly, when increasing deafness made the relation of patient to physician increasingly difficult, patients wanted him to look after them—relying on his kindness, his understanding and his ever ready willingness to obtain for them the advantage of the most recent aids in diagnosis and treatment.

He presented an older tradition of the neurologist, that of one who after years of general practice came into the field of neurology with the background of an intimate knowledge of the more ordinary diseases and a more intimate knowledge of people—the ordinary man, woman and child. He probably never thought of this knowledge and insight under the term "personality understanding" but took for granted that to treat a sick person it is essential to know a great deal about that person. This was as clear to him as was the fact that a nervous or

mental disease is a great deal more than what might be seen under the microscope after death or collected in the laboratory during life.

In his clinical work Frank Fry felt keenly the importance of personality. He also reflected in his attitude toward his patients some of the things that at present are described as the psychobiologic attitude. He did in his way what is being done at present with the aid of a mass of technical investigation and information which was not available to him in his formative years.

The facts of his life are these: He was the son of the Reverend Benjamin St. James Fry and Eliza Dixon Fry. He was a descendant of the Fry family which settled at East Greenwich, R. I., in the seventeenth century. His father was a distinguished clergyman of the Methodist Church and for twenty years was editor of the *Central Christian Advocate,* in St. Louis. Frank Fry prepared for college in the old Smith Academy in St. Louis and graduated from the Ohio Wesleyan University, with the degree of a Bachelor of Arts, in 1877, and of Master of Arts, in 1880. He graduated from the St. Louis Medical College in 1879 and, after a year's internship in the City Hospital, began the practice of medicine. He was demonstrator of anatomy from 1881 to 1888, professor of anatomy from 1880 to 1900 and professor of diseases of the nervous system from 1890 to 1921, when he retired from teaching as professor emeritus of neurology. His preparation for his specialty was largely anatomic, and much of his interest in neurology derived from the fascination of the nervous system in its localization and topographic features.

Dr. Fry was a member of almost all the special societies of neurology and psychiatry and in 1904 was made president of the American Neurological Association, a distinction that reflected the universal acknowledgment of his pioneer work in developing the specialties of neurology and psychiatry in the middle west. Dr. Fry was the first real representative of these specialties in St. Louis. He early established the line between the clinical neurologist and psychiatrist and what was formerly called the alienist. He made it clear by his work, by his published papers and by his presentation of cases and discussions in the medical society that the neurologist and the psychiatrist are something more than a professional adjunct to the courts of law. He further stood for the fact that there is a place in the medical practice of a large city for a man who chooses to devote himself to the study and care of neurologic and psychiatric conditions, much in the same way as the internist or surgeon does in his particular field. This was a radical departure from the customary attitude of alienists in the territory in which Dr. Fry's influence extended. He demonstrated that it is possible for a trained physician to practice the specialties of neurology and psychiatry divorced entirely from the ownership of private sanatoriums and separated from the

technical and legal demands of courts of law. He also showed through his work that the best preparation for a man of this sort is steady contact with the problems of internal medicine. This should be emphasized as Fry's distinctive contribution. He was primarily a clinical neurologist and psychiatrist, and as such he lived his life in active contact with hospital, clinic and private patients.

I could find among Dr. Fry's papers no bibliography of his published contributions. They were chiefly clinical and were scattered throughout many western medical publications. His clinical papers were clear and to the point and left the reader with a distinct impression of the clinical entity which was described. He brought to the attention of general practitioners throughout his part of the country many of the rare and less known types of organic neurologic conditions. He wrote on Parkinson's disease, progressive muscular atrophy and unusual types of tabes dorsalis, multiple sclerosis and other characteristic lesions of the central nervous system which are not the customary material seen in clinics and hospitals. He was particularly interested throughout his later professional life in problems of paresthesias and had devoted a great deal of earnest study to the interpretation of this sensory phenomenon. He had many interesting ideas on the subject of sensation which have not found their way into published articles. As can be seen from this brief sketch of Frank Fry's early training, he never lost interest in and never was unconcerned with the part played in the production of nervous diseases by internal medical conditions. The experience of his early life gave him a fundamental insight into at least the clinical recognition of all kinds of internal medical diseases. He was frequently able to help his patient not merely by understanding the importance of these things but by planning common sense methods of treatment.

He was particularly hospitable and friendly to the young men who came to St. Louis to follow his specialty. There is scarcely any one there in the field of neurology and psychiatry who can fail to remember the encouragement and friendliness of Dr. Fry in the early period of his practice.

In the death of Frank Fry St. Louis loses a worthy and much beloved figure. Through the long period of his actual practice he was a friend and medical adviser to his patients, a generously minded colleague to his fellow practitioners and thoughtful and scholarly in his attitude to his own specialty. He leaves behind a beautiful memory.

SIDNEY I. SCHWAB, M.D.

News and Comment

FIRST INTERNATIONAL CONGRESS OF CHILD PSYCHIATRY

The First International Congress of Child Psychiatry will be held in Paris, France, July 24 to Aug. 1, 1937, under the auspices of the Committee of the International Exposition of Paris. The opening meeting will be held in the Maison de la Chimie, 28 rue Saint-Dominique, Paris (VII), at 9:30 a. m. The congress will convene at the same place for formal discussion at 9 a. m., on July 26, 27 and 28. Visits to various training schools and other institutions and points of interest have been arranged.

There are two forms of membership in the congress—active and associate. The former class of members have the right to take part in the discussions and will receive a copy of the transactions. Physicians are eligible only to this class of membership, but it is not necessary that active members be doctors of medicine. The fee for this class of membership is 125 French francs. Associate members may attend the meetings but cannot take part in the discussion and do not receive a copy of the transactions. The fee for this membership is 75 French francs.

Requests for information and admission to membership should be addressed to Dr. Crimbert, 11 rue Duroc, Paris (VII), France.

AMERICAN PSYCHIATRIC ASSOCIATION

The Ninety-Third Annual Meeting of the American Psychiatric Association will be held at the William Penn Hotel, Pittsburgh, May 10 to 14, 1937.

AMERICAN NEUROLOGICAL ASSOCIATION

The Sixty-Third Annual Meeting of the American Neurological Association will be held at the Ambassador Hotel, Atlantic City, N. J., June 3, 4 and 5, 1937.

Abstracts from Current Literature

Physiology and Biochemistry

LECTURES ON MOTOR ANOMALIES OF THE EYES. ALFRED BIELSCHOWSKY, Arch. Ophth. **13**:569 (April) 1935.

In this article associated paralysis of the parallel lateral movements of the eye and paralysis of convergence and of divergence are discussed. Anatomically, a supranuclear lesion usually causes paralysis of the associated muscle groups of the eyes. The few exceptions are paralyses caused by a lesion in the posterior longitudinal bundle or in the immediate neighborhood of the nuclei of the oculomotor nerves. Such a lesion can deprive one internal rectus muscle of the faculty of adduction in lateral movements, leaving intact its function of convergence, or can render both elevator muscles of one eye unable to produce a voluntary elevation without disturbing the involuntary elevation noted in Bell's phenomenon. Theoretically, supranuclear paralysis of the other individual muscles of the eye is conceivable, but there is no way of differentiating between them because the other muscles do not act as parts of different mechanisms to the same degree as the internal rectus muscle acts in lateral and convergence movements or as the elevator muscles act in opening and closing the eyes. With these few exceptions, the diagnosis of a supranuclear lesion is based chiefly on bilateral and equal paralysis of associated muscle groups.

In uncomplicated cases of this type, both eyes, being unable to move to the right, for instance, are slightly deviated to the left. The deviation induces the patient to turn his head a little toward the paralyzed side. No diplopia is present because of the equality of the deviation on the two sides. Strict proof of the supranuclear origin is given by the intact function of convergence of the left internal rectus muscle. In the case of paralysis of gaze to the right the patient is unable to turn the left eye in only in conjugate movement to the right. In such a case one must consider whether the paralysis of the right external rectus muscle is caused by a supranuclear lesion. It is possible that a lesion of the nucleus of the right abducens nerve involves also the posterior longitudinal bundle, so that the left internal rectus muscle loses its associated function with the right external rectus muscle. This can be decided when the response of the right abducens nerve to a vestibular stimulus is examined.

By far the most frequent of the associated paralyses of vertical movements are paralyses of the elevator muscles; next in frequency are paralyses of the elevator and depressor muscles, and rarest are paralyses of the depressor muscles alone. In some cases Bell's phenomenon is the only proof of the supranuclear origin of paralysis of vertical movements and of the integrity of the nuclei. This phenomenon consists in the ability to move the eyes upward or downward only when the eyes are closed. Then maximum elevation is obtained. This is certain proof of the supranuclear localization of the lesion.

As long as the paralyzed muscles respond to vestibular stimulation it may be assumed that there is integrity of the nerves, their nuclei and the pathways connecting them with the vestibular apparatus. Although in many instances a patient with this type of paralysis is unable to turn his eyes either on command or spontaneously in the direction of an object or a sound, he can do so if he is at first confronted with an object and then asked to follow it in the required direction. How this following movement is released and where the innervation concerned arises is still an unsolved problem. Since there are several centers in the cerebral cortex which are concerned with associated movements, some authors have supposed that the innervations causing the following movement and the willed or commanded movement are derived from different centers and pathways, so that a lesion which interrupts the pathway descending from the frontal lobe makes the voluntary movement disappear while the following movement may not

be disturbed. However, many patients, although they are able to follow a moving object, lack the ability to make an attraction movement, i. e., to turn the eyes toward an outlying object the image of which is situated in the periphery of the retina. Both kinds of movements belong to the so-called psycho-optic reflexes because, being produced by visual stimuli, they are performed more or less instinctively, so that one is justified in placing the origin of these movements in the occipital lobes. In spite of the fact that the attraction movement alone can be lost and not the following movement it is not necessary to assume the existence of separate centers and pathways for them.

It may be possible to make an approximate localization of the lesion causing associated paralysis in an individual case. "Pseudo-ophthalmoplegia," so called by Wernicke since he saw it as a part manifestation of pseudobulbar paralysis, displays the following characteristics: The patient is unable to move his eyes at a word of command, but they are moved involuntarily in states of emotion or if he is interested in an object or in a sensory excitation derived from an object. The following movements can be produced provided the patient's attention is attracted to the moving objects. The reflex movements of vestibular origin are undisturbed. In some of these cases the whole oculomotor apparatus, including the cortical centers, is undamaged, the lesion being transcortical and damaging the connections between the frontal oculomotor centers and other parts of the cortex. Similar symptoms occur in diseases of the extrapyramidal system.

More frequently one encounters a second group of associated paralyses, characterized by inability not only to move the eyes in a certain direction voluntarily or on command but also to move them toward an object which is attracting the patient's attention. The following movement and the reflex movements of the eyes can, however, be produced. In this group the lesion is to be localized below the cortex; probably the pathways descending from the frontal centers are injured not far above the nuclear region.

In a third group the paralyzed associated muscles react only to reflex stimulation; neither the voluntary and attraction movements nor the following movement can be produced. In cases of paralysis of lateral movements the internal rectus muscles are able to perform the convergence movement; in case of paralysis of the vertical movement the elevator muscles may be able to function in Bell's phenomenon. In such cases the lesion must be localized close to the nuclei, the posterior longitudinal bundle being intact.

In a fourth group the paralyzed muscles respond neither to visual nor to other sensory stimuli nor to command, nor are they able to perform a following or reflex movement. In such cases either the posterior longitudinal bundle or the nuclei themselves must have been injured. The latter supposition is untenable in cases of paralysis of lateral movements if the internal rectus muscles are able to produce a convergence movement and in cases of paralysis of the vertical movements if Bell's phenomenon is undisturbed.

In the last group of associated paralyses there are not only symptoms of a supranuclear lesion but also signs and symptoms indicating an injury of the nuclei, such as paralytic squint and diplopia and a variation in the mode of action of the paralyzed muscles according to the mode of stimulation.

In the second part of the paper paralysis of convergence and divergence is considered. Since the internal rectus muscles may be paralyzed for associated lateral movements without loss of convergence function, it seems obvious that the latter function can also be lost without prejudice to the former. It is not known where the convergence center is located. Since convergence paralyses are frequently caused by lesions in the region of the corpora quadrigemina, a subcortical convergence center is presumed to be in that region; isolated lesion of this center or of the pathway descending to the nuclei of both the internal rectus muscles must produce the symptoms of a pure convergence paralysis. There is crossed diplopia for near objects, whereas objects at a distance of more than 1 meter are seen single provided the convergence paralysis is not complicated by exophoria. Even a slight degree of exophoria causes insuperable crossed diplopia

for distant objects if convergence is completely abolished. The angle of deviation is the same when the patient looks straight forward or to either side, but it is increased not only when he looks at near objects but also, as a rule, when he looks up, and is decreased when he looks down. Variations of the signs and symptoms occur according to whether there is complete paralysis or only more or less considerable weakness of the convergence function.

True convergence paralyses of organic origin are rare. Many of the published cases are certainly functional. Insufficiency of convergence occurs as a true functional neurosis in anemic and delicate persons or in patients convalescing after exhaustive illnesses and also in patients with general neurasthenia or hysteria.

To make sure that lack of convergence is a true paralysis of organic origin, the following conditions must be fulfilled: There must be symptoms of an organic intracranial disease; the convergence paralysis must have occurred rather suddenly; the signs and symptoms tested at various times and by various methods must in a certain measure be constant, and the accommodation and convergence reaction of the pupils must be producible without the corresponding convergence.

Concerning the divergence paralysis of Parinaud, oculists are still at variance. Some have confirmed his observations. Others have opposed the concept. Bielschowsky concludes that theoretically the possibility of the occurrence of divergence paralysis must be conceded. He agrees that there are certain conditions which may be confused with divergence paralysis. Destruction of fusion as a result of a physical or psychic shock, and esophoria, previously undiagnosed, may become manifest and display symptoms similar to those of a divergence paralysis.

SPAETH, Philadelphia.

THE CONDUCTION OF CORTICAL IMPULSES TO THE AUTONOMIC SYSTEM. E. A. SPIEGEL and W. C. HUNSICKER JR., J. Nerv. & Ment. Dis. **83**:252 (March) 1936.

It seemed important to Spiegel and Hunsicker to ascertain whether the pyramidal tracts can conduct corticofugal impulses to the autonomic system. In a first series of experiments the motor cortex and the anterior part of the frontal lobe were stimulated after severance of the centrifugal fibers of the hypothalamic vegetative centers. In a second series of experiments the conduction of cortical impulses to the vegetative organs was studied after transverse section of both pyramidal tracts. A transverse section through the cranial part of the pons and the midbrain, severing the central gray matter around the ventricle, the posterior longitudinal bundle and the adjacent dorsal reticular formation, interrupts centrifugal pathways from the hypothalamic vegetative centers, as described by Beattie, Brow and Long.

Spiegel and Hunsicker carried out these experiments on thirty-five cats and obtained the following observations: Section of the centrifugal fibers arising in the hypothalamus impairs the conduction of corticofugal vegetative impulses in a higher degree than does section of the pyramidal tracts, particularly in the case of the pupil and less markedly in the case of the vasomotor nerves and sweat glands. The reaction of the bladder to stimulating or inhibitory cortical impulses was well preserved after severance of the hypothalamic pathways. Study of pupillary innervation showed that the hypothalamic systems carry continuous tonic impulses to this organ, while no such influence of the pyramidal tracts could be found, at least in cats, as the myosis that followed severance of the extrapyramidal systems was lacking after section of the pyramidal tracts. Observations on innervation of the bladder in bilateral lesions of corticofugal pathways are of interest because the bladder is under voluntary control. Bilateral severance of the pyramidal tract in cats did not prevent the conduction of corticofugal stimulating or inhibitory impulses to the bladder, an observation which is easily understood when one remembers that the pyramidal tracts are much less important in quadrupeds than in man.

HART, Greenwich, Conn.

ON THE "SYNDROME OF THE PREMOTOR CORTEX" (FULTON) AND THE DEFINITION OF THE TERMS "PREMOTOR" AND "MOTOR," WITH A CONSIDERATION OF JACKSON'S VIEWS ON THE CORTICAL REPRESENTATION OF MOVEMENTS. F. M. R. WALSHE, Brain **58**:49, 1935.

A development in recent clinical and experimental studies of the grasping phenomena seen in association with certain lesions of the frontal lobes is the formulation by Fulton and his collaborators of a syndrome of the premotor cortex. They believe that both in man and in apes a characteristic group of motor disorders meriting this title is to be observed. The evidence submitted in support of this hypothesis is mainly experimental and consists in observations made on apes after circumscribed cortical ablations, but this evidence has recently been supplemented by that obtained in a clinical case of glioma of the frontal lobe, which, they believe, confirms the conclusions reached from experiment and warrants their application to man. It is the opinion of Walshe that neither on anatomic nor on physiologic grounds can Fulton's division of the structure and function of the cortical region lying anterior to the fissure of Rolando be accepted.

By motor area, Fulton and his collaborators mean that part of the precentral convolution adjacent to the fissure of Rolando in which are found the giant cells of Betz. The premotor area lies immediately anterior to it.

The direct clinicopathologic evidence for the so-called premotor syndrome of Fulton in man consists so far in a single case. The lesion was a glioma of the frontal lobe, the component signs appearing in what Fulton and his collaborators thought to be a characteristic and pathognomonic sequence. These signs in order of appearance were: gradually increasing awkwardness in an extremity, affecting more particularly highly integrated digital movements; early appearance of spasticity and increase of tendon jerks; forced grasping; late appearance of weakness of grasp and other gross movements, and vasomotor disturbances of the affected part. No special clinical studies of a syndrome of the true motor cortex are recorded by Fulton, but he believes that when this develops progressively its signs are as follows: generalized weakness of the extremity, especially of grasp, appears precociously; spasticity, if present at all, appears late; there is no forced grasping. Acute lesions of this region produce flaccid paralysis and depression of reflexes.

The syndrome of the premotor cortex as described, with the exception of forced grasping, represents a sequence of events and signs common to every progressive hemiplegia. The syndrome of the motor cortex as described does not call up in the clinical observer's mind anything with which he is familiar. No distinction between generalized weakness or loss of power as described in the syndrome of the motor cortex and loss of skilled movements of the fingers as described in the syndrome of the premotor cortex can be drawn. A limb can do naught else than move, and the expression loss of power can have no meaning other than loss of movement. The presence or absence of spasticity cannot be used to differentiate the two syndromes, since the rate of development of the lesion and its progressive or stationary character are factors which enter largely into the matter.

In the case reported, the forced grasping is the only component sign of the syndrome which may be confidently ascribed to involvement of the premotor region. The hemiplegia must be assumed to be a consequence of interference with the functions of the motor cortex and its projection system, of which it is a typical symptom, unless it can be proved that the lesion was in fact wholly confined to the premotor region and was incapable of provoking neighborhood symptoms in the contiguous motor region. This cannot be proved, for the lesion was a cystic astrocytoma which pointed in the frontal cortex just anterior to the ascending frontal convolution. One cannot know to what degree the motor cortex was infiltrated by growth or its function disturbed by edema or reactionary changes. In man, therefore, the evidence adduced does not support the occurrence of such a syndrome of the premotor cortex as has been described by Fulton.

The generalization that "general weakness," flaccidity and depression of reflexes are the characteristics of ablation of the motor cortex is not in accord with the

facts as recorded by Horsley, Leyton and Sherrington, and also by Fulton and his collaborators. Horsley's case of cortical ablation (1909) in man fulfills the conditions of a planned experiment on an animal. The patient suffered from violent athetoid movements of the right arm, and when his limb was quiet he presented no abnormalities of movement or reflexes. The arm area was carefully delimited and excised. The immediate results were disappearance of athetosis and total loss of voluntary power in the limb. The return of voluntary power followed the usual course, the final result being permanent impairment of skilled purposive movements in the hands and fingers, with some hypertonus in the paralyzed parts. Leyton and Sherrington's findings concerning isolated ablation of the arm area in the chimpanzee are identical with those just recorded as ocurring in the human subject. The observations of Fulton and Kennard are also essentially identical with these, though their summary and conclusions do not indicate the fact.

In the chimpanzee unilateral ablation of the premotor area is followed immediately by total flaccid hemiplegia (Fulton and Kennard, 1932). This is followed in a few days by feeble forced grasping and some resistance to passive movement. Within a week nothing is seen but a lag in the initiation of voluntary movement.

Bilateral ablation of the frontal lobes to the anterior border of the motor cortex results in a striking lack of spontaneity and bilateral forced grasping, but no spasticity and no paralyses. As may be seen in the human subject, the presence of forced grasping is not necessarily accompanied by spasticity, a finding which does not confirm Fulton's association of these two phenomena as integral components of the premotor syndrome and suggests that after all the appearance of spasticity as a residual requires and depends on a lesion of the motor cortex or of its projection system.

Thus it appears that Fulton's generalization that "grave postural and motor disturbances" follow ablation of the premotor cortex scarcely conveys an accurate impression. In macaques, unilateral ablation has no visible effect (Richter and Hines, 1932) and in the chimpanzee the fugitive hemiplegia is probably a neighborhood symptom. Forced grasping in this animal is transient, and the sole residual defect is that which Jacobsen (1932) noted on examining a chimpanzee trained with a problem-box after the fugitive paralysis resulting from ablation of the premotor cortex had passed off; the animal appeared unable to organize the necessary manipulations and had to relearn them.

Combined unilateral ablation of the motor and premotor cortex merely produces a more severe degree of hemiplegia than does ablation of the former area alone, together with the appearance of forced grasping. Fulton suggests that the spasticity of residual hemiplegia in man is due to the addition of a lesion of the premotor projection system to a lesion of the pyramidal tract, but the recent examination by Davidson and Bieber (1934) appears to render this view untenable. One may conclude, therefore, that the sole symptom safely to be attributed to destroying lesions of the premotor cortex is forced grasping, and this in turn, as Richter and Hines have shown, is conditional on the integrity of the corpus callosum. All the other symptoms must be ascribed to disturbance of function in the motor cortex and its projection path. That they are all constantly produced by ablation of this area of the cortex confirms this conclusion. Further, it appears probable that apraxia may be a residual effect of ablation of the premotor cortex.

In further consideration of the syndrome of the premotor cortex, the precise meaning to be attached to the terms motor and premotor is of importance. When Fulton and his collaborators use the term motor area they have in mind the area gigantopyramidalis, which they have assumed to be coterminous with the physiologically delimited motor cortex. As a corollary, all that cortical region lying between the anterior limits of Campbell's intermediate precentral area and the area gigantopyramidalis becomes the premotor area. This last-named area has its own extrapyramidal projection system, the pyramidal tract being relegated

to the area gigantopyramidalis. It seems clear that the very existence of a physiologically differentiated premotor cortex and also that of the syndrome of this cortical area depend on the accuracy of this identification of a physiologic with a cyto-architectonic entity. If, in fact, the motor area, properly so named, is more extensive than this assumption allows, the premotor area with its functions and its syndrome is largely swallowed up by the motor area. The solution of the question involves a consideration of both anatomic and physiologic evidence.

Fulton's motor area takes in that part of the precentral convolution adjacent to the fissure of Rolando in which are found the giant cells of Betz. This corresponds approximately to Campbell's precentral area, to Brodmann's area 4 and to Economo's area gigantopyramidalis. The premotor area lies immediately anterior to it. It corresponds to Campbell's intermediate precentral area, to Brodmann's area 6 and to Economo's area frontalis agranularis. Brodmann includes his areas 4 and 6 within his area precentralis, which he correlates with the physiologic motor cortex. Economo expresses a similar view, and Campbell alone identifies the area gigantopyramidalis with the motor cortex of the physiologist. Leyton and Sherrington (1917) have shown that the true motor cortex has no sharply defined anterior limit. The anterior boundary, as determined by them, varied somewhat from specimen to specimen but appeared to lie for the most part in the intermediate precentral area of Campbell.

It is clear, therefore, that the identification of the area gigantopyramidalis, or even of the entire precentral area, with the motor cortex of the physiologist is erroneous, since the last-named area includes a considerable extent of the histologically delimited intermediate precentral area. Parallel with the assumption that the motor cortex, properly so called, is identical with the area gigantopyramidalis is the assumption that the pyramidal tract arises solely from giant cells within this area. Horsley (1909) gave adequate reasons for rejecting such an assumption, stating that to restrict the term motor to Campbell's precentral area, as he wished, would exclude the motor center for the muscles of the face, larynx, pharynx and eye as well as a part of the representation of movements of the head. Limitation of the motor area to the region of the giant Betz cells disregards the anatomic rule that an efferent or motor cell varies in size according to the distance the axon has to travel in the central system.

There are other reasons for rejecting the restriction of the pyramidal tract to the axons of the giant cells in the Betz cell area. The fact that the Betz cells lie solely within this area is proof that the pyramidal tract arises only within it. Holmes and Page May (1909), while accepting the giant cell origin of the pyramidal tract, also accept wide variations in size for these cells. The area of distribution of these cells in man and in the chimpanzee they believe is more extensive in an anteroposterior direction than is seen in the cortical maps of Campbell and Economo.

The statement that the giant cells alone give rise to pyramidal fibers has no meaning unless it is agreed what constitutes a giant cell. The giant cell is a dimensional and not a physiologic entity, and one can scarcely blame the histologist if it has come to be regarded as the latter. Finally, the recent investigations of Hoff and Hoff (1934) indicate that the area 6 of Brodmann and Campbell's intermediate precentral area also furnishes fibers to the pyramidal tract.

In short, the hypothesis that the pyramidal tract derives solely from cells within the area gigantopyramidalis is as unfounded as that which identifies this area with the motor cortex of the physiologist. Both run counter to experimental and histologic facts of observation. The terms motor and premotor are not interchangeable with the terms precentral and intermediate precentral, and the conception of two sharply differentiated cortical regions, each with its own projection system and each with widely differing functions, is illusory. The true motor cortex includes much of Fulton's premotor area, and the pyramidal system arises within all parts of it.

Various views as to what is meant by the expression cortical representation of movement compete for existence. On the one hand is the view exemplified in the writings of Campbell and adopted by Fulton. The essential feature of this

conception of cortical motor representation is that this embodies two distinct mechanisms, each coterminous with a distinct cyto-architectonic field, each with its own separate functions and each sharply circumscribed by anatomic boundaries. At the other extreme is the view taken by Lashley, in which any topographic localization of function in the cortex is frankly regarded as a fiction. Between these two extremes stands the conception of cortical representation formulated by Jackson. He conceived three levels of function, the highest represented by the prefrontal region and the middle level represented by the excitable motor cortex of the physiologist. The middle level has been evoked out of the lowest level, and in it are represented, or recoordinated, the simple and general movements represented in the lowest level. There are no abrupt localizations in these two levels, and all movements are widely represented throughout them. Jackson's theory of the cortical representation of movements postulates no jig-saw puzzle of rigidly defined, separate local elements on the one hand, nor an undifferentiated cortex acting by mass on the other. These opposing notions might almost be defined as being differentiation without integration and integration without differentiation, respectively. Jackson's conception allows of the special representation of every possible movement, and is compatible alike with the absence or paucity of symptoms after local destroying lesions and with the spread and sequence of convulsion in states of instability of gray matter. It truly represents differentiation with integration and would appear to be the only possible valid generalization of all the varied facts of clinical and experimental observation.

SALL, Philadelphia.

THE FRONTAL LOBE IN MAN: A CLINICAL STUDY OF MAXIMUM REMOVALS. WILDER PENFIELD and JOSEPH EVANS, Brain **58**:115, 1935.

Penfield and Evans studied three patients after resection of the frontal lobe. The first case was one of a calcified oligodendroglioma of the right frontal lobe. The amputation was carried back to within 1 cm. of the motor gyrus all the way down to the lowest frontal gyrus. From this line it passed across cleanly to the midline, so that the septum pellucidum and the anterior 2 or 3 cm. of the sectioned corpus callosum were visible after removal. In the second case, removal of the left frontal lobe for a cerebral cicatrix was carried to within 1 or 2 cm. anterior to the precentral gyrus. In its lower limit the line of removal crossed Broca's convolution not far from the anterior end of the fissure of Sylvius. At the base of the hemisphere the line of removal skirted closely the posterior edge of the orbital plate and lesser wing of the sphenoid bone. In case 3, only about half the frontal lobe was removed for a cerebral cicatrix.

It was found that extensive amputations of the frontal lobe produce surprisingly little disturbance of function which can be detected by ordinary means of examination. There is no disturbance of the control of micturition, no forced grasping and no alteration of tone of the extremities or of the activity of deep or superficial reflexes. The removal in the second case produced a partial loss of the patient's capacity for oral mental arithmetic as distinguished from written. This patient also had an unexplainable absence of dizziness and past pointing after rotation and caloric tests, even though the vestibular function was otherwise normal.

In the two cases (case 1 and 2) in which more extensive removal was done the patients presented certain important defects in common. These defects are considered by the authors to have begun at the time of origin of the initial lesion and merely to have become complete at the time of the operation. By ordinary psychometric tests the patient would have to be judged normal, although neither would rank very high. Each patient was lacking in initiative but was very good natured and cooperative, which may be evidence of a lack of initiation of ideas. Insight and capacity for introspection were preserved. Capacity to follow instruction was not impaired, but initiative and capacity for planned action were clearly defective. This was especially true in case 1; the patient had become incapable of choosing for herself possible courses of action. If others presented to her the

possibilities, she made up her mind easily, and when a task lay before her there was no reluctance or hesitation in undertaking it.

The removal of the anterior half of the right frontal lobe in case 3 was not associated with any detectable neurologic or psychologic alteration.

SALL, Philadelphia.

ANALYSES OF BLOOD GASES IN LESIONS OF THE BRAIN. E. KLEMPERER, Arch. f. Psychiat. **103**:214 (May) 1935.

The work reported in this paper is a continuation of work previously reported by Klemperer. Analyses were made of the blood of sixty-six patients suffering from different types of organic disease of the brain. In order to be certain that the diagnoses were correct, the author waited for three years after the completion of the work, checking up on the subsequent history of each patient. Determinations of the carbon dioxide and oxygen contents and of the total capacity of the blood in terms of volume per cent were made. The specimens of blood were taken from each arm sixteen hours after the last meal, the veins being approximately symmetrical. The determinations were made according to the Van Slyke method; two determinations were made, the mean of the two being used as the final figure.

The findings were as follows: In cases of unilateral lesions without aphasia, the oxygen content of the blood from the affected arm was either normal or slightly subnormal and that of the blood from the other arm was somewhat lower; there were no appreciable differences in the carbon dioxide content. In cases of unilateral lesions with aphasia the findings were practically the same, with the exception that with an increase of the sensory components in the aphasia the oxygen content fell. In cases of sensory aphasia without hemiplegia the findings fell into two groups: one in which the oxygen content of the blood was normal in the right arm and low in the left arm and the carbon dioxide content was low in each arm, and one in which the oxygen content showed a pronounced increase on the right and was distinctly higher on the left, while the carbon dioxide was decreased on the left, with less change on the right. No consistent results were found in cases of motor aphasia. In cases of lesions of the thalamus the affected arm showed a very low oxygen content, with either decreased or normal findings on the other side; the carbon dioxide changes were not significant. In cases of anosognosia a decrease in oxygen content was found in the affected arm, and a somewhat higher content in the other arm. Again the carbon dioxide was not appreciably changed. In cases of multiple sclerosis the only important change was decreased carbon dioxide content in the blood taken from the healthy side. In cases of parieto-occipital lesions there was a very low oxygen content on the diseased side, with a somewhat higher but subnormal content on the other side; the carbon dioxide contents were mostly increased. In cases of disease of the basal ganglia there were very low oxygen contents, even in cases in which other parts of the brain were also affected. In cases of parkinsonism there was a decreased oxygen content on the affected side, with a somewhat higher, but still subnormal, content on the other side; the carbon dioxide content was, if anything, increased on both sides. Similar findings were also obtained in cases of torsion spasm. The patients with chorea were divided into two groups: (*a*) those who were very restless and tense and showed a marked increase in the oxygen content of the blood, higher on the diseased side, and a very low carbon dioxide content on both sides, and (*b*) those who had a low oxygen content on both sides and a practically normal carbon dioxide content.

MALAMUD, Iowa City.

REFLEX INFLUENCES ON THE EXCRETION OF WATER AND SODIUM CHLORIDE. S. JANSSEN, Arch. f. d. ges. Physiol. **235**:523, 1935.

Severance of the vagus nerve and ligature of the carotid or the femoral artery reflexly induce polyuria and an increase in the concentration of sodium chloride in the urine. These reflexes are not abolished by destruction of the renal nerves. The extrarenal effectors through which these reflexes act were not determined.

SPIEGEL, Philadelphia.

FUNCTION OF THE OTOLITHS, STUDIED BY MECHANICAL STIMULATION OF THE UTRICULAR OTOLITH IN THE LIVING PIKE. H. ULRICH, Arch. f. d. ges. Physiol. **235**:545, 1935.

The otolith of the utriculus was stimulated by a standardized hair. Such stimulation induced reflex tonic ocular movements. Pressure on the otolith in the anterior and outward direction elicited deviation of the homolateral eye upward and backward, and in the outward direction, vertical (upward) deviation. The contralateral eye moved in the opposite direction. Pressure on the otolith inwardly was ineffective. Rotation about the longitudinal axis of the body to the left stimulated the left labyrinth only, and rotation to the right, the right labyrinth only.

SPIEGEL, Philadelphia.

Neuropathology

SUBACUTE FORM OF OPTIC NEUROMYELITIS IN A PATIENT WITH SYPHILIS. A. RADOVICI and M. PETRESCO, Encéphale **30**:271, 1935.

Radovici and Petresco report the case of a man aged 42 who presented rapidly developing paraplegia, with exaggerated tendon jerks, ankle clonus, tendency to flexion, a Babinski sign bilaterally, diminished abdominal reflexes, and hypesthesia to touch, pain and temperature in the lower part of the thoracic, the lumbar and the sacral territory. Examination of the cerebrospinal fluid showed positive Wassermann and Nonne-Apelt reactions and 10 lymphocytes per cubic millimeter. Cisternal injection of iodized poppy-seed oil revealed no block. There was a history of a positive Wassermann reaction of the blood five years earlier, followed by repeated series of treatments with mercury and bismuth. The patient was addicted to the use of alcohol and tobacco in excess. The course of the illness was rapid. In spite of therapy with arsenic and bismuth, paralysis and hypesthesia extended to the upper limbs. There was retention of urine. The patient fell into a state of continuous somnolence; he was disoriented and hallucinated. He wept and shouted. He died five months after the onset of paraplegia.

Anatomic examination showed diffuse leptomeningitis, with infiltration of round cells and macrophages in the meninges of the whole central nervous system, predominating in the posterior sulcus of the cord and over the optic chiasm. There was diffuse lymphoplasmocytic infiltration, in some situations pluristratified, of the adventitial spaces of the small and medium vessels, with punctate hemorrhages. The media, the internal elastic membrane and the intima were spared. In areas where the infiltration was most intense—in the globus pallidus, the infundibulum, the tuber cinereum, the pituitary stalk and the lower limit of the medulla—the vessels were surrounded by diffuse infiltration and edema of the parenchyma, with small patches of demyelinization and alteration of the ganglion cells. There were, in addition, large plaques of demyelinization, without gliosis, in the optic chiasm and at numerous levels of the cord, predominating in the posterior and lateral funiculi. A large zone of necrotic softening occupied the second and third thoracic segments. In this region the cord was flattened, diffluent and grossly structureless. Microscopically, the ganglion cells were reduced in number and were shrunken, chromatolytic and mostly anucleate. Glia cells were rare and pyknotic. The myelin tubes were preserved but showed a granular structure, as in the beginning of degeneration. There was no vascular infiltration.

These lesions were not of the syphilitic type, for the characteristic endovasculitis was absent. They are differentiated from the lesions of multiple sclerosis by the absence of glial proliferation and by the necrosis, from the lesions of epidemic neuraxitis by the integrity of the midbrain and the presence of demyelinization and necrosis, from the lesions of the subacute necrotic myelitis of Foix and Alajouanine by the absence of vascular hypertrophy with stratified proliferation of the media and intima and from the lesions of Schilder's periaxial encephalitis by the integrity of the white substance of the hemisphere. However, Guillian, Alajouanine, Betrand and Garcin, as well as Marinesco and his collaborators, have reported cases of periaxial encephalitis with lesions of the cord similar to those reported in the present case.

LIBER, New York.

GLIAL CHANGES IN THE CEREBRAL CORTEX AT A DISTANCE FROM A TUMOR OF THE BRAIN. F. SUAREZ LOPEZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:383 (March) 1935.

Lopez studied glial changes in the brain at a distance from a cerebral neoplasm. He investigated twenty-three cases—nine of intracerebral tumor, six of extracerebral tumor, five of metastatic tumor of the brain and three of cyst which was not neoplastic. Four cases used as controls were investigated at the same time. In the normal brains used as controls astrocytes were rarely observed in the molecular layer. There was a slight increase in the number of astrocytes in the brains of the older subjects used as controls. In these normal brains the astrocytes retained their delicate processes, with only a mild tendency to formation of fibers. The astrocytes were somewhat more numerous in the deeper layers, especially at the junction of the gray and white matter. Lopez also observed physiologic differences in the number of glia cells in various parts of the brain.

The most striking observation in this investigation was that of the proliferation of the astrocytes in the molecular layer far from the site of the tumor. This hyperplasia was more marked in parts of the cortex deep in the sulci. This was most evident in cases of primary intracerebral tumor. The astrocytes seemed larger than normal and showed structural changes such as thicker and coarser protoplasmic processes, as well as a tendency to transformation into fibrous astrocytes. Groups of three or four astrocytes were seen in the slides, probably owing to the frequency of division of these cells. The astrocytic changes were less marked, though present, in the cases of primary extracerebral tumor. Occasionally similar glial proliferation was observed in the deeper layers of the cortex. In such cases the glial changes were in parts of the brain near the tumor and were absent in sections taken at a distance from the neoplasm. No astrocytic proliferations in the molecular layer were observed in the group of metastatic tumors or in the nonneoplastic expanding lesions.

Lopez ascribes the diffuse glial changes to the influence of a toxic factor associated with the growth of the neoplasm, as well as to the effects of prolonged increased intracranial pressure. The absence of glial changes in some of the primary tumors and in the metastatic tumors is explained by the relatively short duration of the disease. The peculiar distribution of the glial changes in the most superficial layers of the cortex favors its connection with prolonged increased pressure of the spinal fluid. The glial changes are not an attempt at repair, for no degeneration of the ganglion cells was demonstrable in the areas of glial proliferation. Lopez believes that the glial proliferation is a reversible process.

SAVITSKY, New York.

ALLYLISOPROPYLACETYLCARBAMIDE (SEDORMID) POISONING. A. H. FORTANIER, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:494 (April) 1935.

A case of allylisopropylacetylcarbamide (sedormid) poisoning with pathologic changes is reported. A woman aged 52, during a period of depression with paranoid features, took fifty-one tablets of allylisopropylacetylcarbamide, with suicidal intent. She was found in coma seven hours later. On her admission to the hospital she was stuporous, and there were no focal signs of disease of the nervous system. The pupils were miotic and did not react to light; the ankle and knee jerks were present; the plantar reflexes were not elicited, and the corneal reflex was absent bilaterally. She died about two days after her admission, of terminal bronchopneumonia. Postmortem examination revealed congestion of the internal organs and foci of bronchopneumonia in both lungs. There were acute enlargement and inflammation of the paratracheal glands. The right kidney was absent, owing to a former nephrectomy, and the left kidney showed compensatory hypertrophy. The brain presented no gross changes.

Microscopic examination of the brain showed changes in the ganglion cells of the brain stem in the region of the substantia reticularis and in the vagal and pontile

nuclei and marked transformation of the Nissl substance, with degenerative changes, in the nuclei of these cells. The bodies of the ganglion cells in these regions were swollen, and the cellular margins were frequently poorly delineated. In the swollen cell bodies Fortanier observed structures which stained metachromatically with the Nissl stain. He believes that these metachromatic granules are identical with the products of albuminoid degeneration described by van der Horst. Similar changes in the ganglion cells were observed in the mesencephalic region, the thalamus and the striatum, though they were much less pronounced than in the brain stem. No changes occurred in the cerebral cortex. A mild glial reaction was seen in these regions, mainly in the nature of neuronophagia, with an occasional isolated area of gliosis. Perivascular infiltration with a few plasma cells was rare.

This pathologic picture is strikingly similar to that in cases of intoxication with somnifen (the diethyldiallylbarbiturate of diethylamine) described by van der Horst, though it is perhaps less marked because of the longer duration of the illness of van der Horst's patients. Fortanier comments on the fact that drugs other than barbiturates can show selective action for nuclei of the brain stem.

SAVITSKY, New York.

ACUTE AMAUROTIC EPILEPSY IN MACACUS RHESUS. LUDO VAN BOGAERT and HANS JOACHIM SCHERER, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:757 (May) 1935.

During the course of two months van Bogaert and Scherer observed a hitherto undescribed affection of the nervous system in Macacus rhesus monkeys. It was characterized by insidious onset and a relatively rapid course, ending in death in two instances in six and eight days, respectively. The third animal was killed on the third day. Two of the monkeys recovered. The clinical picture was characterized at its onset by restlessness, clumsiness, unsteadiness of gait, undue irritability and fearfulness. Blindness and epileptic convulsions were noted soon after the onset. The skin became coarse and the lips dry, and epileptic convulsions increased in frequency and intensity, so that the slightest stimulus precipitated a seizure. Two of the animals died during a convulsion. Fever was present in only one case. Toward the end of the course the animal lay helpless on the ground and was totally blind. No anemia or gastro-intestinal or pulmonary symptoms were present.

Clinical examination of the animals showed unsteadiness of gait in the early stages. The authors concluded that incoordination was probably secondary to amaurosis. *Mouvements de manège* were noted. These were always in the same direction and were accompanied by coarse horizontal nystagmus. The epileptic convulsions began as clonic seizures, with a rather protracted tonic phase, followed by marked postconvulsive torpidity. Amaurosis was present, with mydriasis. There was loss of pupillary reflexes. The fundi were normal. Mydriasis was usually related to waves of irritability and the epileptic seizures. The tendon reflexes were normal, except for the absence of the ankle jerk in one instance. The abdominal reflexes were present. Muscular power was apparently good. Plantar stimulation produced a flexor response.

Attempts to transmit the disease to healthy animals were unsuccessful. An emulsion of the medulla oblongata of one of the monkeys was injected into an animal of the same age and species. The animal showed no mental, neurologic or visual disturbances.

Histologic examination of all three brains showed scattered leukocytic infiltration of the meninges, the cells being observed more often in the outer layers of the meninges near the dura, and diffuse proliferation of astrocytes in the molecular layer of the cortex, not related in intensity to the overlying meningeal infiltration. The microglial reaction was less marked in other layers of the cortex. The changes in the white matter consisted of recent glial changes about the blood vessels and even gross breaking down of the white matter and widespread glial collections around the blood vessels resembling the nodules of typhus fever. Severe injury to the

occipital cortex, differing somewhat in each instance, was one of the most striking features. The tissue alterations were in the nature of marked necrobiotic, ischemic areas in two of the brains and marked glial and vascular proliferation, with parenchymatous degeneration, in the third. In the animal with the most acute infection, which died after three days, there was diffuse leukocytic infiltration of the cortex, most marked in the occipital region. In the animal with the most protracted course vascular proliferation was diffuse, but there was no leukocytic infiltration, and in the third animal, which was killed on the fourth day, there was neither diffuse vascular proliferation nor evidence of inflammation in the cortex. The author emphasizes the important difference in the three cases.

The vascular proliferation, parenchymatous degeneration and leukocytic infiltration are all considered independent, concomitant reactions to the toxic or infectious process responsible for the diffuse cerebral changes. That parenchymatous degeneration and inflammatory changes in reaction to the same noxious agent can occur in the same subject has already been proved in cases of dementia paralytica. There is no anatomic ground for the hypothesis that the necrobiotic changes are secondary to functional circulatory changes accompanying the epileptic seizures. The cornu ammonis and the cerebellar cortex were free from these necrobiotic changes.

The authors conclude that these five cases were representatives of the same disease and that the process can be considered a variant of a spontaneous disease in monkeys. No septic focus was observed in the body. The process is either infectious or toxic. An adequate knowledge of the diseases of monkeys is important for evaluation of the results of experimental transmission of human virus diseases to these animals.

SAVITSKY, New York.

Psychiatry and Psychopathology

A FOLLOW-UP STUDY OF HOCH'S BENIGN STUPOR CASES. H. L. RACHLIN, Am. J. Psychiat. **92**:531 (Nov.) 1935.

Benign stupor, as described by Hoch, consists of the syndrome of apathy, inactivity, negativism and thoughts about death. It was supposed to be a form of manic-depressive psychosis and derived its name from the hypothesis that the outcome was clinically favorable. Rachlin has had the opportunity of examining thirteen of Hoch's original patients after a lapse of from fifteen to thirty years from the time the cases were first reported. He found that eleven had been readmitted to state hospitals, most of them as having schizophrenia. It is Rachlin's opinion that benign stupor is not a clinical entity but merely a catatonic stupor occurring in young persons.

DAVIDSON, Newark, N. J.

DYNAMIC CONCEPTS AND THE EPILEPTIC ATTACK. S. E. JELLIFFE, Am. J. Psychiat. **92**:565 (Nov.) 1935.

The epileptic disturbance can be thought of as occurring at three levels of organization. Modern medicine has focused attention chiefly on the first of these levels, inadequately on the second and not at all on the third. Indeed, neurologists have set up an almost fanatic resistance against any analysis of the symbolic significance of the convulsion. Yet the epileptic personality clearly is a manifestation of sadistic and aggressive drives, while the fit itself represents the triumph of the death instinct, destroying itself and destroying the future. Jelliffe believes that Hughlings Jackson, if he were alive today, would have accepted the freudian concept of the dissolution of symbolic patternings as an analog of his understanding of the release process. The similarity between an epileptic attack and the beginning of a paroxysm of pertussis suggests to Jelliffe that both are symbolic reactions to an agency which has threatened the life instinct.

DAVIDSON, Newark, N. J.

SUMMARY OF THE REPORT OF THE AMERICAN NEUROLOGIC ASSOCIATION COMMITTEE FOR THE INVESTIGATION OF STERILIZATION. ABRAHAM MYERSON, Am. J. Psychiat. **92**:615 (Nov.) 1935.

Myerson deplores the circulation of the myth that the normal population of the world is being swamped by the feebleminded. He points out that the mentally deficient have a lower birth rate and a higher death rate than the normally intelligent and that there is no reason for the fear that the former are crowding the latter out of the world. He cites a list of persons of abnormal or psychopathic personalities who were of great value to society and without whom the world would have been poorer. The warmth of character and aggressiveness of the person with hypomania, for example, often makes him a useful citizen, so that efforts to prevent the perpetuation of manic personalities are of doubtful social good. The committee disapproves of the sterilization of persons who are themselves normal, in order to prevent the birth of potentially psychopathic offspring; it also disapproves of using character or morality as a criterion of eligibility for sterilization. The importance of environmental agencies in precipitating psychopathic conditions is also stressed in the report. If any sterilization law is adopted, it should be applicable to inmates of state and private institutions alike, and no law should enforce sterilization without the consent of the patient.

DAVIDSON, Newark, N. J.

MENTAL DISEASE AMONG FOREIGN-BORN WHITES, WITH SPECIAL REFERENCE TO NATIVES OF RUSSIA AND POLAND. BENJAMIN MALZBERG, Am. J. Psychiat. **92**:627 (Nov.) 1935.

Criticizing the thesis that certain racial stocks have inbred psychopathic traits, Malzberg points out that one of the items often cited as evidence of the inborn inferiority of certain immigrant groups suggests an opposite conclusion. Thus, it is often said that the longer a racial group remains in the United States the less likely are its members to show mental instability; that is, the longer ago a group immigrated to this country the more stable its descendants are. If it were true, however, that the psychopathic tendency is racially inborn, one ought to find the same incidence of mental disturbance in successive generations of the same stock. The fact that this incidence falls seems to indicate that the environmental factor, adjustment to the American cultural pattern, is a responsible force. A detailed analysis of the incidence of mental disease among foreign-born persons of Polish and Russian stock illustrates this, for when due allowances are made for differences in age, Malzberg's tables show that these groups had mental morbidity rates below the average for other foreign-born stocks. The incidence of psychopathic conditions is higher among American residents born in northwestern Europe than among those born in Russia or Poland. If there is any inheritance of mental instability, it is through family stocks, not racial groups.

DAVIDSON, Newark, N. J.

ANDROGYNOID CHARACTERISTICS IN A CASE OF SCHIZOPHRENIA. ANNETTE C. WASHBURNE, Am. J. Psychiat. **92**:641 (Nov.) 1935.

Defining androgynism as a swing toward a feminine personality in a male, Washburne cites a case of dementia praecox illustrating transvestism and androgynoid features. A white man aged 23, single, had a history of a moody, irritable, shut-in personality. At the age of 21 he began to steal the hats, dresses and underclothes of his mother and sister and seemed to enjoy wearing them. On one occasion he wore a woman's bathing-suit on a beach. These excursions were accompanied by seminal emissions, with incomplete erections. He often had outbursts of rage directed against his mother. The facies was effeminate, and the hair sparse. The skin was soft and white, and the breasts and buttocks were enlarged. Testes, penis and prostate were those of a normal man. Neurologic and ophthalmologic examinations gave normal results, but an encephalogram disclosed moderate internal hydrocephalus, with cortical atrophy. Eventually, the

patient deteriorated. The author suggests a psychoanalytic interpretation of the psychosis, describing the rages against the mother as a punishment of one who represented what he desired to be but could never attain.

DAVIDSON, Newark, N. J.

RELATION OF TRAUMA TO MENTAL DISEASE. ABRAHAM MYERSON, Am. J. Psychiat. **92**:1031 (March) 1936.

Psychiatrists are frequently called to testify as to the relationship between an accident and subsequently developing dementia praecox or manic-depressive psychosis. Since these diseases are both constitutional and the causes are unknown, Myerson is reluctant to indicate any causal relationship between an environmental stress and the psychosis. In the case of manic-depressive psychosis, however, it is reasonable to assume that a serious emotional disturbance followed promptly by a psychotic state in a previously normal person may well be an aggravating or precipitating etiologic factor. On the other hand, trivial traumas, which to the patient himself have little emotional meaning, cannot be accepted as causative of the psychosis in any sense. With dementia praecox the chance of a cause and effect relationship is even less. This psychosis runs its course independently of any environmental force, and the relationship must be vivid before Myerson will admit the possibility that the trauma may have aggravated a latent psychosis or precipitated an episode of insanity.

DAVIDSON, Newark, N. J.

A PSYCHOANALYTIC STUDY OF THE SIGNIFICANCE OF SELF-MUTILATIONS. KARL A. MENNINGER, Psychoanalyt. Quart. **4**:408, 1935.

In self-mutilation the destructive tendencies are turned back on the subject, not as in suicide, on the whole (with which is usually coupled a wish to die) but on part of himself. Menninger illustrates the situation with the history of a depressed young woman who first killed her own child and then permitted her arm to be amputated by a train and became well. In this case the child represented the patient's mother, whom she hated; the sacrifice of the arm was an atonement for the murder of the child (mother). Although this case shows some of the dynamics of self-mutilation, it does not answer other problems, such as: (1) What is the reason for the increased power of the destructive element and for its direction back on the self? (2) What is the significance of the sacrifice? (3) Why is a particular part of the body sacrificed?

In order to answer these questions Menninger considers self-mutilation as observed in the neuroses, religious practices, pubertal rites, psychoses and organic diseases and, among normal persons, the conventional practices of nail-cutting, hair-cutting and shaving. All these examples show a fairly consistent pattern of motives.

Self-mutilation represents the surrender or repudiation of the active rôle; i. e., the physical removal or injury of parts of the body represents castration, and this direct or substitutive sacrifice of the genitals appears to satisfy certain erotic and aggressive cravings and, at the same time, to gratify the need for self-punishment by a self-inflicted penalty. The aggressive element may be active, as when a person mutilates himself as a representation of an introjective object whom he hates, or it may be passive, as when the mutilation is done to exasperate some one else. The erotic gratification achieved by the surrender of the active in favor of the passive rôle is dependent on innate bisexuality and the unconscious envy of the male for the female rôle. There often is secondary gratification by exploiting the results of the mutilation.

Self-punishment atones by sacrifice for former aggressive acts and wishes and provides an anticipatory protection, as though to forestall future punishment and permit further indulgences by the advance payment of a penalty. Self-mutilation is the result of a conflict between aggressive impulses aided by the superego and the will to live; i. e., it is a form of attenuated suicide to avert complete self-destruction.

PEARSON, Philadelphia.

PSYCHO-ANALYSIS OF SPACE. PAUL SCHILDER, Internat. J. Psycho-Analysis **16**:274 (July) 1935.

Schilder challenges the notions of philosophers and psychologists who think only of the space outside of the body, without taking into consideration the space which is filled by the body. Body space is senseless without an outward space. The experience of space can be changed by drug intoxication and is also found in the experience of patients with schizophrenia.

The perception of space as disclosed by psychoanalysis is partially dependent on psychologic structures which belong to the ego, in spite of the organic foundation. They are deeply dependent on tonic functions which are in close connection with the vestibular apparatus and postural and righting reflexes, but these can be influenced by psychologic attitudes. Libidinous conflicts of the hysterical type provoke, by conversion, changes in the perception of space. Size, direction and distance can become the expression of specific libidinous situations. According to the general analytic structure of hysteria, the spatial relations are changed according to the genital relations to other persons. The hysterical changes in space perceptions are often the symbolic expression of the relations to the genitals as such and to total personalities who are images of parents. In cases of obsession neurosis and compulsion the sadistic attitudes lead not only to destructive tendencies concerning the love objects and isolated parts of their bodies but to distortions of space as a whole and isolation of its parts. Similar phenomena can be observed as the expression of the sadistic attitudes in cases of depression. The narcissistic regression observed in schizophrenia provokes disintegration of spatial experiences in which the body space and the space of the outward world melt into each other. Space perception thus becomes an immediate expression of the libidinous situation. These mechanisms are illustrated by the histories in several cases.

Space perception is the expression of the function of the ego and the id and their relation to each other.

KASANIN, Chicago.

THE GENESIS OF THE FEELING OF UNREALITY. C. P. OBERNDORF, Internat. J. Psycho-Analysis **16**:296 (July) 1935.

Oberndorf continues his studies on depersonalization, stressing the erotization of the process of thinking. He traces the development of the feeling of unreality (depersonalization) to an attempt to repress a previous identification. The child has previously identified itself with the "thinking" parent after being rebuffed by the dull parent. The process of thinking becomes erotized and assumes a feminine or masculine cast. "The feeling of unreality occurs when an attempt is made to repress such thinking as incompatible with the thought (and action) considered normal for the individual." The loss of the repressed part of the personality leads to a feeling of unreality. A narcissistic wound to the ego and superego in the form of prolonged loss of libidinal satisfaction is considered a contributory factor in depersonalization. Attention is called to the relationship that exists between unreality, the feeling of stupidity and the deepest forms of thought block. In treatment the libido must be deflected from thinking into emotional response.

The sequence of events in a typical case of unreality is as follows: Identification at the oedipus level with the parent of the opposite sex, emphasis on thinking as a masculine trait, psychic equation of head and phallus, indulgence in thinking as a pleasurable, sexually stimulating activity and the development of the state of unreality when the patient attempts to adapt himself to the type of thinking (and action) regarded as normal for his sex.

A case is reported in detail to illustrate the thesis of the paper. The patient as a child received little affection from the parents. She was the youngest of four sisters, and before her birth a boy was expected. She had shown marked homosexual tendencies since the age of 7 years. In adolescence she experienced difficulty in assuming femininity. She turned to abstract thinking as a source

of "active thrilling pleasure" (erotization of thought). She considered thinking a masculine attribute and identified herself with her father, who was a successful scientist. She also became expert in her father's recreational activities—trap-shooting, horseback riding and photography. Even after marriage she continued her scientific studies for two years. When she ceased her scientific studies, the feeling of unreality became more intense. The feeling of unreality first developed when the patient began seriously to contemplate marriage. Her "body went through the movements of becoming engaged, but she was just not along." Later, during childbirth the same phenomenon occurred; her body, not she, gave birth to the child. The patient was partially restored to her feminine rôle as a real person by making conscious the influence of her unconscious homosexuality.

KASANIN, Chicago.

PHALLIC PASSIVITY IN MEN. R. LOEWENSTEIN, Internat. J. Psycho-Analysis **16**:334 (July) 1935.

Certain disturbances of potency, such as collapse or total absence of erection, occur frequently under special circumstances, such as when the woman gives the slightest show of resistance. In other cases coitus is impossible unless the woman not only consents but takes the initiative. The inhibition which causes such a phenomenon is due to fear of castration; this fear is associated with certain episodes in early childhood. If the inhibitions imposed in childhood were severe, the man wants, more or less, the woman's permission to have intercourse. In such cases the woman has to demonstrate her willingness several times and even extend it to such important details of the sex act as the introduction of the penis into the vagina. The fact that some men experience an orgasm during masturbation or fellatio indicates that the inhibition is concerned only with active penetration.

Phallic passivity corresponds to that early form of male sexuality, when the child wants to be caressed, looked on, petted or touched. In the development of sexuality the desire to penetrate appears much later. The stage of phallic passivity is a normal step in the development of the child, and if the castration feelings are normally resolved the boy goes on through other phases to normal sexual development. Fixation at a passive stage obviously predisposes to passive homosexuality.

KASANIN, Chicago.

CONTRIBUTION TO THE STUDY OF COMPARATIVE PSYCHIATRY. M. SEREJSKI, Arch. f. Psychiat. **103**:510 (July) 1935.

This article is a report of a neuropsychiatric survey of four of the north Caucasian tribes which was undertaken by Serejski with the help of a number of collaborators. The study was carried out on the basis of a house to house search for signs and symptoms indicative of any type of mental or neurologic aberrations, supplemented by studies of the heredity and of the social environment. The present report is concerned particularly with the psychiatric problems and considers the various types of psychoses and neuroses observed in these people.

The same types of psychoses were observed that are seen in other localities, but the symptomatology was definitely different. Schizophrenia was the most prevalent type of disease; it was found mainly in the catatonic form. There were a pronounced poverty of speech and a scarcity of delusions and hallucinations, but in spite of that the prognosis was poor. Next in frequency was epilepsy, with a preponderance of twilight states, deterioration, hallucinations and hyperkinesia. Here, too, the prognosis was poor. Another type of mental disease that was encountered is designated as schizo-epilepsy. In this disease there was either an onset with symptoms of schizophrenia of the catatonic type, followed by the development of more or less typical epileptic attacks, or vice versa. Of the toxic and infectious psychoses Serejski discusses neurosyphilis, in the form of dementia paralytica and of syphilis of the central nervous system. The first was characterized by ideas of grandeur and epileptiform attacks, and the second, by diffuse intellectual deterio-

ration, hallucinations and a malignant course. Epidemic encephalitis was characterized predominantly by hyperdynamic symptoms, convulsions and impulsive behavior. Rabies was of a particularly malignant type, even if prophylaxis was used. It is of interest to note that although drinking is very common, there were practically no alcoholic psychoses. There were also no involutional psychoses observed. The manic-depressive syndrome was represented only in the manic form, with ideas of grandeur and psychomotor overactivity. There were no depressions, no self-derogatory ideas and no suicidal attempts. The neuroses were represented mainly by the hysterical type with a preponderance of the so-called introverted type of neuroses in the form of depressive and anxiety states. Traumatic neuroses were almost absent and psychasthenias rare. It was interesting to note that whereas the psychoses were most frequent in men, the neuroses were just as predominant in women.

MALAMUD, Iowa City.

Meninges and Blood Vessels

CAVERNOUS SINUS THROMBOSIS OF DENTAL ORIGIN. BERNARD P. MORGENSTERN, Arch. Otolaryng. **21**:442 (April) 1935.

Three cases of thrombosis of the cavernous sinus following dental infection are reported. In all typical symptoms developed, although autopsy was performed in only one case. Infection occurs by way of the pterygoid plexus, with retrograde thrombosis through a small emissary vein connecting directly with the cavernous sinus or through the branch from the inferior ophthalmic vein, which in turn runs into the cavernous sinus. Still another possibility is that a septic embolus from the pterygoid plexus may go from the posterior facial vein to the anterior facial vein and by reversed current to the angular and ophthalmic veins to the cavernous sinus.

HUNTER, Philadelphia.

THE MECHANICS OF DELIVERY ESPECIALLY AS IT RELATES TO INTRACRANIAL HEMORRHAGE. FREDERICK C. IRVING, New England J. Med. **214**:635 (March 26) 1936.

According to the records of the Boston Lying-in Hospital for the past ten years, there were 20,827 deliveries, with intracranial hemorrhage in 1 of 107 births. Deaths from intracranial hemorrhage have shown a steady drop since 1932, being 5.2 per thousand births in that year, 3.8 in 1933 and 2.5 in 1934. Intracranial hemorrhage may be due to trauma, intra-uterine asphyxia or hemorrhagic disease of the new-born. Many believe that the chief cause is violence or unskilful operative delivery. In 20 per cent of infants on whom autopsy was performed intracranial hemorrhage was due not to trauma but either to asphyxia or to hemorrhagic disease of the new-born.

Petechial hemorrhages scattered through the various organs are a recognized pathologic picture in cases of asphyxia of the new-born. Asphyxia may result from prolonged and unprogressive second stage of labor, the fetal heart being thrust for many hours against an unyielding perineum. While the obstetrician can do nothing to prevent hemorrhagic disease, he can diagnose the condition and begin treatment.

Trauma may result from an attempt to deliver an infant which is too large through a pelvis which is too small. By far the most frequent source of fatal injury is delivery through an undilated cervix; more babies lose their lives from this cause than from attempts to overcome bony obstruction. The use of analgesic drugs in labor will assuage the pains of labor and make the attendant more willing to await the workings of nature.

It is evident that danger from a skilfully performed low forceps operation is slight but that the risk increases steadily the higher the station of the head in the pelvis.

MOORE, Boston.

ACUTE BENIGN LYMPHOCYTIC MENINGITIS (ACUTE ASEPTIC MENINGITIS). W. R. F. COLLIS, Brit. M. J. **2**:1148 (Dec. 14) 1935.

A type of acute benign meningitis, which is distinct from serous meningitis, is described. Two cases of acute aseptic meningitis are cited. The syndrome has previously been described as follows: The onset is acute; the patient rapidly becomes gravely ill; all the usual signs and symptoms of meningitis occur, and the temperature is increased at first but returns to normal after the first week. The disease is of short duration; it is benign and is not followed by complications. The spinal fluid findings are characteristic. The fluid is sterile and contains from 150 to 250 lymphocytes, while the sugar and chloride contents are normal. Collis suggests the name "acute benign lymphatic meningitis" as an accurate term for the condition. This allows for the possibility of a virus as the causal agency.

BECK, Buffalo.

EPIDURAL HEMORRHAGE DUE TO HEMOPHILIA CAUSING COMPRESSION OF SPINAL CORD. W. M. PRIEST, Lancet **2**:1289 (Dec. 7) 1935.

Priest reports a case of spontaneous epidural hemorrhage in the upper part of the spinal canal, causing compression of the cervical region of the cord. Neurologic complications of hemophilia, due to spontaneous hemorrhage into the nervous system, are uncommon. A man aged 27 was admitted to the hospital with a history of acute pain in the neck, legs and back, of sudden onset, for twenty-four hours. When it began he was unable to bend his back or even to move. He also complained of painful swellings in the left wrist joint and on the right shin, just above the ankle. There was no history of trauma. It was learned that in 1925 a "swelling" over the right tibia and albuminuria had been present. In 1926 he had severe, prolonged hemorrhage following the extraction of teeth. In 1930 a hematoma appeared in the right thigh and recurred five months later; in the same year he had hemorrhages into the left knee and the right rectus abdominis muscle. Since 1930 there had been repeated hemorrhages into the thigh and calf muscles, knee joint and left elbow. There was no family history of hemophilia.

Examination revealed a swelling over the left wrist and a tender firm swelling over the crest of the right tibia; no tenderness was present over the spine, but great pain was caused by its flexion or extension. All tendon reflexes were present except the right ankle jerk. There was poorly sustained left ankle clonus. The plantar responses were extensor, more markedly on the left. The urine was loaded with albumin but contained no blood. The cerebrospinal fluid was clear but deep yellow. The total protein content was 1.2 mg. per hundred cubic centimeters. There were 4 white and 9 red cells per cubic millimeter. The bleeding time was one minute and fifty seconds, the clotting time seventeen minutes and the platelet count 232,000. The patient's condition gradually improved, being interrupted from time to time by hematoma in some part of the body. He was discharged in May 1934 without symptoms. The bleeding time was essentially unchanged, but the clotting time was reduced to thirty seconds. Lumbar puncture revealed a normal fluid. The total protein content was only 0.04 mg per hundred cubic centimeters. Since the patient's general condition was good at all times, transfusion was not considered necessary.

WATTS, Washington, D. C.

Diseases of the Brain

TUBEROUS SCLEROSIS IN THE INFANT. JOSEPH H. GLOBUS and HERMAN SELINSKY, Am. J. Dis. Child. **50**:954 (Oct.) 1935.

Globus and Selinsky present two cases in children aged 4 and 5 months, both of whom began to have frequent, generalized, convulsive attacks before their admission to the hospital. Both had appeared normal at birth but soon showed evidences of abnormality. After their admission to the hospital, there was a transient

febrile state, and in one case this was apparently associated with infection. Postmortem study in both cases showed the pathologic changes characteristic of tuberous sclerosis. The authors conclude that with the meager and vague clinical data present in most cases it is impossible to recognize this disease in young infants but that convulsive seizures and mental retardation associated with blindness and maldevelopment or tumor formation in some other part of the body justify in many instances a suspicion that the disease may be tuberous sclerosis.

WAGGONER, Ann Arbor, Mich.

CHOKED DISC IN SYPHILIS OF THE NERVOUS SYSTEM. BERNARD J. ALPERS and JOSEPH C. YASKIN, Am. J. M. Sc. **190**:333 (Sept.) 1935.

Five cases in which syphilis of the nervous system caused choked disk are presented. Severe frontal headache and dimness of vision were present in all five instances and progressive loss of hearing in one ear in three cases. Choked disk was the most constant sign, being as great as 5 diopters in four cases; deafness occurred in two instances and unilateral ptosis with partial weakness of the inferior rectus muscle in one case. Abnormal visual fields were present in three cases; the Argyll Robertson pupil was lacking in all. The Wassermann reaction of the blood and the spinal fluid were positive in four cases; there was pleocytosis in four cases, the number of cells (lymphocytes) ranging from 36 to 107. The diagnostic criteria are: (1) absence of localizing signs and the variability of those signs present; (2) a consistently positive Wassermann reaction of the blood and usually pleocytosis and a positive Wassermann reaction of the spinal fluid, and (3) a response to antisyphilitic treatment. The underlying lesion is probably basilar meningitis. The management of the choked disk is well illustrated by the individual treatment in the cases, varying from antisyphilitic treatment alone to fever therapy and craniotomy. The prime consideration is the preservation of the patient's eyesight.

MICHAELS, Boston.

ACUTE VASOSPASTIC HYPERTENSION: A CASE WITH SIGNS OF CEREBRAL IRRITATION AND SEVERE RETINITIS WITH REMISSION. NORMAN M. KEITH and HENRY P. WAGENER, Am. J. M. Sc. **190**:454 (Oct.) 1935.

A woman aged 31 had been under observation for twenty years. In 1921 migrainous headaches appeared for the first time. In 1932 she had increasingly severe headaches. The blood pressure was 220 systolic and 140 diastolic. Two weeks later a peculiar stuporous, semiconscious mental state developed, with left homonymous hemianopia. The cerebrospinal fluid was under a pressure of 25 cm. of water, and hypertonic solutions were administered, with apparent benefit. Typical retinitis of so-called hypertension, with constriction of the arterioles to grade 2 or 3, was present. It is assumed that an acute angiospastic process was present, similar to that associated with hypertensive toxemia of pregnancy, with resultant ischemia and anoxemia of the retina. The mental state may have been due to cerebral angiospasm, which is of interest in view of the history of previous and subsequent attacks of migraine with hemianopia.

MICHAELS, Boston.

DIFFERENTIAL DIAGNOSIS BETWEEN CEREBRAL HEMORRHAGE AND CEREBRAL THROMBOSIS. CHARLES ARING and HOUSTON MERRITT, Arch. Int. Med. **56**:435 (Sept.) 1935.

Aring and Merritt report an analysis of the clinical data in 245 cases of lesions of the cerebral vessels confirmed by necropsy. The following clinical features suggest the occurrence of hemorrhage rather than of thrombosis: severe headache, vomiting or coma at the onset, convulsions, progression of the illness after the onset, extremely high blood pressure, abnormalities in the eyes, stiffness of the neck, a Babinski sign bilaterally, high spinal fluid pressure, grossly bloody spinal fluid and a high leukocyte count in the spinal fluid. The period of survival is usually shorter in cases of cerebral hemorrhage than in those of cerebral thrombosis. In

50 per cent of the cases of cerebral hemorrhage the patients died within four days of the onset, and in only 28 per cent of the cases of cerebral thrombosis did the patient die within this period. Peripheral arteriosclerosis was found more often and more extensively in cases of thrombosis. The average age of the patients at the onset was 59 in cases of cerebral hemorrhage and 64 in cases of cerebral thrombosis; 57 per cent of the former and 33 per cent of the latter group of patients were in coma at the onset. Convulsions were more common (15 per cent) in the cases of cerebral hemorrhage than in those of cerebral thrombosis (7 per cent). Most of the patients with cerebral hemorrhage (51 per cent) vomited at the onset, whereas only 6 per cent of those with cerebral thrombosis had this symptom. Severe headache was noted ten times as often (60 compared with 6 per cent) in the group with cerebral hemorrhage. The systolic pressure was greater than 200 in 41 per cent of the cases of cerebral hemorrhage and in only 26 per cent of the cases of cerebral thrombosis. Dilatation of the contralateral pupil was noted in one fourth of the patients with cerebral hemorrhage and in only one seventh of those with cerebral thrombosis. Stiff neck was recorded in more than half (55 per cent) of the former and in only 7 per cent of the latter series. The spinal fluid findings are important in making a differential diagnosis. A fluid pressure in excess of 400 mm. of water or 31 mm. of mercury was found in 16 per cent of the cases of cerebral hemorrhage and in none of those of cerebral thrombosis. A spinal fluid pressure of more than 200 mm. of water (15 mm. of mercury) was recorded in 65 per cent of the cases of cerebral hemorrhage and in only 24 per cent of the cases of cerebral thrombosis. The presence of blood in the fluid is good evidence of cerebral hemorrhage.

Because of the difference in treatment and prognosis the classification of a vascular accident as cerebral hemorrhage or cerebral thrombosis is important. With proper care, this differentiation may usually be made during life.

DAVIDSON, Newark, N. J.

EPILEPSY SECONDARY TO HEAD INJURY. MARK A. GLASER and FREDERICK P. SHAFER, Arch. Surg. **30**:783 (May) 1935.

A survey of the literature indicates that generalized epileptic convulsions are uncommon sequelae of head trauma. Epilepsy is likely to follow only the more severe head injuries generally associated with fracture of the skull; in such cases the most likely incidence of epilepsy is about 2.5 per cent. It occurs most frequently from six months to two years after the injury and less frequently from two to seven years afterward. Convulsions developing within the first six months after minor head injuries should be considered of psychogenic origin. Encephalographic study is advised in all cases from the standpoint both of possible therapeutic value per se and of indicating suitable cases for operation. SPERLING, Los Angeles.

THE RÔLE OF THE CEREBRAL CORTEX IN NARCOLEPSY: THE CLASSIFICATION OF NARCOLEPSY AND ALLIED DISORDERS. MAX LEVIN, J. Neurol. & Psychopath. **15**:236 (Jan.) 1935.

A classification of narcolepsy and allied disorders is attempted on the basis of Pavlov's work showing that sleep is a state of inhibition radiated over the cortex and that the probable function of the sleep center is to regulate the frequency, depth and duration of sleep. Disturbances of sleep may be due to involvement either of the sleep center or of the cortex. In cases of morbid somnolence without signs of "localized sleep" no distinction is as yet possible. In cases of narcolepsy and allied disorders in which there are signs of localized sleep with or without morbid somnolence, the cortex is most likely at fault. The four principal signs of localized sleep are cataplexy, sleep paralysis, attacks of powerlessness occurring without relation to sleep or emotion and increased motor activity during sleep. Sleep paralysis is that paralysis occurring while the patient is lapsing into or coming out of slumber, the patient being conscious, and illustrates, as do all forms of localized sleep, the dissociation of the substrates of motility and of consciousness. SPERLING, Los Angeles.

TWO CASES OF SUBDURAL HEMATOMA. PAUL VAN GEHUCHTEN and J. MORELLE, J. belge de neurol. et de psychiat. **35**:213 (April) 1935.

Van Gehuchten and Morelle report two cases of subdural hematoma, the first in a man aged 58, with no history of trauma but with a syndrome of intracranial hypertension and mental changes characterized by disorientation and agitation. The patient presented increased reflexes and a Babinski sign bilaterally. A ventriculogram showed the presence of a lesion on the left side. At operation a subdural hematoma was observed. The second case was that of a woman aged 51, with a history of symptoms for a year, with repeated falls, the last of which, occurring one month before examination, was associated with a short period of unconsciousness. After this there gradually appeared paralysis of the right side with distinct signs of pyramidal involvement and mental disturbance characterized by incoherence and disorientation. There was no evidence of increased intracranial pressure, but the spinal fluid was xanthochromatic. In the second case autopsy revealed a subdural hemorrhage on the left and rather diffuse pachymeningitis without hemorrhage on the right. The authors discuss possible factors in the development of such a condition. They assume that in most cases internal hemorrhagic pachymeningitis is due to trauma, followed by secondary development of pachymeningitis, but they also think that in some instances the pachymeningitis appears first and is followed later by hemorrhage. They believe that this is proved in the second case, in which a characteristic subdural hematoma was present on the left, while on the right there were features characteristic of internal pachymeningitis without hemorrhage. On the nonhemorrhagic side there was thickening of the arachnoid, with large blood spaces. The authors believe that trauma may cause rupture of the relatively fragile wall of these lacunar spaces, followed subsequently by hemorrhage. They assume therefore that most commonly pachymeningitis is present and that subdural hemorrhage is secondary to this after trauma, but they also assume that chronic subdural hematoma may develop directly after trauma without a preexisting arachnoid lesion.

WAGGONER, Ann Arbor, Mich.

MENTAL DISORDERS SYMPTOMATIC OF MENINGEAL HEMORRHAGE. H. BAONVILLE, J. LEY and J. TITECA, J. belge de neurol. et de psychiat. **35**:305 (June) 1935.

The authors report two cases of subarachnoid hemorrhage and state that mental disorders are of great frequency in the course of meningeal hemorrhages. In the majority of cases the patients are said to be somnolent, apathetic and indifferent to the surroundings, presenting a syndrome of depression with slowing of the intellect. This syndrome may be accompanied by disturbances of orientation, memory, particularly recent memory, and attention and by mental confusion. The most constant mental disturbance is loss of memory. A man aged 47 exhibited euphoria, emotional indifference, mental slowness, palsy of the right side of the face, exaggeration of the tendon reflexes in the right arm, clonus of the right foot, some difficulty in walking and albuminuric retinitis and papilledema. From the somatic standpoint he had marked arterial hypertension, increase in the size of the heart, arteriosclerosis and a small liver. The diagnosis was established by lumbar puncture. The next patient, a man aged 43, had had disturbances of sensation and transient pareses for eighteen months, when there suddenly developed mental disturbance characterized by agitation, disorientation, loss of memory and attention, mental slowing and visual and auditory hallucinations. The tendon reflexes were increased, except the achilles jerks, which were diminished. The diagnosis in this case was likewise established by lumbar puncture.

The authors call attention to the importance of diagnosis of the etiology of the hemorrhage; they find that among possible etiologic factors the syphilis and tuberculosis are primary but that other infectious diseases, such as typhoid, recurrent fever, pneumonia, tetanus, grave icterus, measles, smallpox and German measles, may also be causes. They state that meningeal hemorrhage may occur in

the course of intoxication, such as that caused by alcohol, strychnine, lead or uremia. Different affections of the central nervous system may be complicated by subarachnoid hemorrhage, such as cerebral neoplasm, dementia paralytica, encephalitis and meningitis. Also to be considered are somatic diseases, such as arteriosclerosis, endocarditis and blood dyscrasias. The authors conclude that in 95 per cent of cases the condition is associated with arteriosclerosis, syphilis or nephritis.

WAGGONER, Ann Arbor, Mich.

LINDAU'S ANGIOMA AS A CHARACTERISTIC GROUP OF CEREBELLAR TUMORS. R. JUNG, Arch. f. Psychiat. **103**:580 (July) 1935.

A survey of the literature on Lindau's angioma and of a large number of cases in his own clinic leads Jung to conclude that angiomas of this type form a fairly large group of the generally infrequent cerebellar tumors of adults. During eleven years he found seven cases in which the diagnosis was verified. Clinically the picture is characterized by symptoms referable to the vermis and the medulla, with signs of generalized intracranial pressure and disturbances of posture of the head. There were no pronounced manifestations of a unilateral cerebellar lesion, even though the tumor was always restricted to one hemisphere. The diagnosis can be made only when it is possible to demonstrate an angioma in the retina. Nevertheless, symptoms pointing to a cerebellar tumor in an adult suggest the possibility of an angioma. Swelling of the disks occurs only in some cases and late in the process. Two patients were operated on, with good results. In the other cases death ocurred, even though the general symptoms were mild. The tumor is usually near the cortex of one or the other hemisphere, and extends into the white matter. Histologically there are pronounced proliferation of the vessels, a thick network of mesodermal fibers and a marked deposit of fat in the cells. Mast cells were observed in all cases. Jung suggests that these tumors form a transition from gliomas to vascular growths. Hereditary factors were found in only one case.

MALAMUD, Iowa City.

NEVI OF THE SKIN ASSOCIATED WITH INTRACRANIAL ANGIOMAS AND HYDROPHTHALMOS. G. KREYENBERG and I. HANSING, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:751 (May) 1935.

Kreyenberg and Hansing report three cases of cutaneous nevi associated with intracranial angiomas and hydrophthalmos, with one autopsy. While usually the nevus is on the same side as that of the lesion of the brain, there was also involvement of the skin on the other side in these cases. In each case an extensive nevus of the skin, congenital glaucoma on the side of maximum involvement, jacksonian epilepsy and mental deficiency were noted. Angiomas of the type reported usually arise from vessels of the pia. The affected cerebral hemisphere is usually smaller. Emphasis is placed on the diagnosis of intracranial angiomas during life by means of roentgenography, when calcified vessels are present. Calcification occurs frequently and has proved useful in diagnosis. In the first case such calcifications showed clearly. Thickening of the bones of the skull on the affected side is related to defective development of the underlying hemisphere.

SAVITSKY, New York.

MULTIPLE SCLEROSIS IN TWINS. M. ASTWAZATUROW, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:744 (Sept.) 1935.

Astwazaturow reports the cases of two sets of twins. The first pair were dissimilar twins. The clinical picture was not identical in the two. There was atrophy of the optic nerve in one and none in the other, and the disability and progression were much more marked in one than in the other. When they were first seen in 1927, one had definite disseminated sclerosis, while the other showed

merely diminished abdominal reflexes and a slight difference in the patellar reflexes. The author was disinclined at the time to make a definite diagnosis of multiple sclerosis in this second case and warns of the importance of such minimal clinical findings, especially when there is evidence of the fully developed disease in the other member of the family.

The second pair of twins came for examination when one of them, a medical student, requested an examination for nystagmus. He became concerned about it after hearing a lecture on the subject. Both twins showed nystagmus, diminished abdominal reflexes and mild suggestive signs referable to the pyramidal tract. They were not sick and made no complaints. These clinical findings may be expressions of some constitutional defects for which the author suggests the term "polyscleroid abiotrophy." While they resemble multiple sclerosis, they do not show the same tendency to progression. Astwazaturow is, however, not at all certain regarding the prospects of the later development of multiple sclerosis.

He also cites the case of a girl aged 15 who had mild nystagmus, hyperreflexia on the right and an Oppenheim reflex on the left. Her uncle, aged 39, also presented mild signs such as occur in multiple sclerosis (ptosis on the right, hyperactive reflexes of the upper tendon on the right, hyperactive patellar reflex on the left, mild intension tremor on the left and diminution of the abdominal reflexes on the right. The changes in these two cases were also attributed to a nonprogressive polyscleroid abiotrophic condition, though the author was uncertain regarding the future of the girl. Cases of multiple sclerosis have been reported in a daughter and father. Other members of the same family showed mild signs such as are described in the other cases.

Only two other cases of multiple sclerosis in twins have been reported (Prussak and Legras). The genetic factor in multiple sclerosis was not clear until the publication of the monograph of Curtius in 1933. The reported cases in twins confirm the probability of the importance of heredity in the pathogenesis of multiple sclerosis.

SAVITSKY, New York.

MORBIDITY STATISTICS FOR A CONTROL SAMPLE OF THE POPULATION (SIBLINGS AND PARENTS OF ONE HUNDRED WIVES OF PATIENTS WITH DEMENTIA PARALYTICA IN BERLIN). FRIEDRICH PANSE, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:194 (Nov.) 1935.

Another study is presented as a control in which data gathered in the north of Germany are utilized in order to permit valid conclusions regarding the heredity of mental disease and to rule out the rôle of chance variations. The average age of the wives studied was 45.9 years. There was 1 case of each of the following conditions: cerebral syphilis, tabes dorsalis, hysterical psychopathic state, chorea minor, enuresis nocturna and congenital absence of the vagina. There were 2 cases of each of the following: eccentric personality, irritable psychopathic state, and mental deficiency with a history of infantile convulsions. Five subjects had a constitutional depressive psychopathic personality; 6, migraine, and 5, pulmonary tuberculosis, and 6 were sinistrals. None of the wives had dementia paralytica.

Five hundred and fifty-eight siblings of the wives of patients with dementia paralytica were studied. The infantile mortality was 35.1 per cent, if persons up to the eleventh year were included. There were 13 pairs of twins, making an incidence of 1:50, the average being 1:80. There was 1 case of schizophrenia, an incidence of 0.35 per cent. The incidence of manic-depressive psychosis was 0.44 per cent, and that of epilepsy, 0.82 per cent. The percentage of mental deficiency was 4.15, if persons with the less marked defective states were included. There were 26 persons (7.45 per cent) with psychopathic personalities, none of whom was institutionalized, only 1 with chronic alcoholism and 2 (0.55 per cent of all living patients, excluding infants who died) who committed suicide. Six of the siblings died of tuberculosis. There were 30 violent deaths, probably owing

to the fact that the population concerned was industrial and had participated in the World War. One of the series died of tumor of the brain. The relatively low mortality from tuberculosis was probably due to the average age of the subjects, with a consequent relatively greater mortality from malignant growths. Five had other nervous diseases, such as chorea, sciatica, eclampsia and herpes zoster; 23 (12 per cent), infantile convulsions; 7 (1.9 per cent), enuresis; 9 (2.48 per cent), sinistralism, and 3 (0.83 per cent), goiter.

Of the 200 parents, 1 (0.52 per cent) had schizophrenia; 1 (0.55 per cent), manic-depressive psychosis, and 3 (1.51 per cent), epilepsy; 5 per cent were mentally defective, and there was an equal number of persons with psychopathic tendencies. The incidence of senile psychoses among the parents, counting only persons above the age of 60, amounted to 5.3 per cent, which is much higher than that for any of the previous control groups; chronic alcoholism occurred in 5 per cent, and 2 committed suicide. The mortality from tuberculosis was 5.7 per cent; violent deaths occurred in 2 per cent. The sinistrals numbered 4 per cent. None of the parents had dementia paralytica.

These figures are comparable with those for control groups of the population which came from Basel and Munich. The incidence of epilepsy is high and is accounted for by the higher frequency of epilepsy in northern Germany. The variation in the percentage of persons with psychopathic personalities reported by various observers is due to the uncertain criteria for the diagnosis of this condition.

SAVITSKY, New York.

CEREBROSPINAL SYMPTOMS ASSOCIATED WITH DISEASES OF THE LIVER. TORBEN GEILL, Acta psychiat. et neurol. **10**:245, 1935.

Cerebral disturbances often complicate diseases of the liver. Irritability, delirium, convulsions and eventually coma are common during the terminal stages of acute hepatitis and atrophy and cirrhosis of the liver. Occasionally the cerebral symptoms may dominate the picture to such an extent that when jaundice is absent or slight, the true nature of the condition may easily be missed. Geill cites nine cases in which he made personal observations and disease of the liver was confirmed at autopsy. He discusses the mental and neurologic symptoms present during life. He points out that the cerebral disturbances are likely to develop early and are marked in association with parenchymatous affections of the liver (hepatitis) and usually slight with obstructive jaundice (cholelithiasis and carcinoma of the pancreas). He states that the cerebral symptoms are brought about when the intermediary metabolism of the liver is impaired.

YAKOVLEV, Waltham, Mass.

CATAMNESTIC STUDY OF THE RELATIONSHIP BETWEEN INFANTILE TETANY AND SUBSEQUENT DEVELOPMENT OF EPILEPSY. V. HENDRIKSEN, Acta psychiat. et neurol. **10**:259, 1935.

In 91 per cent of cases at a large institution for patients with epilepsy, the onset of epilepsy occurred before the age of 20 years. Hendriksen investigated the incidence of epilepsy in ninety-seven infants treated for tetany in 1912 and 1913. The investigation was carried out in 1925 and 1926 and was repeated on the same material in 1932 and 1933, when the subjects had reached the age of 20 or over. At the time of the last investigation seven patients had died in infancy of tetany, and ten had died between 2 and 16 years of age. Of the latter, epilepsy had developed in only two; these two patients, however, were also mentally defective. The fate of twenty-nine patients was unknown. None of them had been admitted to the only colony for persons with epilepsy in the state (Denmark). Of the fifty-one remaining persons who were known and living at the time of the investigation, none suffered from epilepsy. Hendriksen concludes that infantile tetany does not lead to epilepsy later in life.

YAKOVLEV, Waltham, Mass.

Diseases of the Spinal Cord

ENCEPHALOMYELITIS FOLLOWING THE USE OF SERUM AND VACCINE. N. WINKELMAN and N. GOTTEN, Am. J. Syph. & Neurol. **19**:414 (July) 1935.

Two cases of encephalomyelitis following the injection of foreign protein are reported. Horse serum was the irritant in one case and a colon b. streptococcus vaccine in the other. Horse serum was given in the first case to control hemorrhage after extraction of a tooth. Signs of cerebral involvement developed three weeks after injection of the serum and a few days after the development of severe coryza. The symptoms included delirium, dimness of vision, hallucinations and aphasia. The patient had a choked disk of the right eye with neuroretinitis, a Babinski sign bilaterally, paralysis of the legs and a level lesion with a definite area of anesthesia. The patient died in a state of sepsis ten weeks after the injection of the horse serum. Autopsy disclosed small round cell infiltration of the spinal leptomeninges, proliferation of glia cells, distention of the spinal anterior horn cells and infiltration of the white tracts with perivascular elements and protoplasmic astrocytes. Throughout the cord were many glial foci. In the brain similar patches of glial infiltration were noted, while throughout the cortex were numerous areas of necrosis with accumulations of gitter cells.

The second patient was receiving injections of streptococcus and colon bacillus vaccine for the treatment of psoriasis. Several hours after the fourth injection there developed nausea, vomiting, chills, fever, backache, urinary retention and diplopia. The pupils became unequal and the tongue tremulous, and a Babinski sign was noted. There was slow improvement, and the patient was able to leave the hospital six weeks after admission.

DAVIDSON, Newark, N. J.

TERATOMA OF THE SPINAL CORD. P. C. BUCY and D. N. BUCHANAN, Surg., Gynec. & Obst. **60**:1137, 1935.

The tumor first caused symptoms at the age of 16 months but was not removed until the child was almost 3 years old and suffering from mixed and alternating spastic and flaccid paraplegia. The tumor was cystic, contained 35 cc. of glairy material, showed a mural nodule and lay within the arachnoid. In common with the ten previously recorded examples of teratoma of the cord, the growth contained ectodermal and mesodermal but no entodermal derivatives. The origin was traced to the posterior columns at the caudal end of the cord.

HUNTER, Portland, Ore. [ARCH. PATH.]

PAPILLOEDEMA CAUSED BY A CERVICAL CORD TUMOR. DOUGLAS MCALPINE, Lancet **2**:614 (Sept. 14) 1935.

The occurrence of papilledema in association with tumor of the cervical cord is rare. One case has been reported by Carlill and Carling and another by Davis. Papilledema associated with syringomyelia has been described by Alpers and Comroe.

McAlpine's case occurred in a woman aged 20, who was first seen by him on July 20, 1934. In June 1932 she had noticed aching pain in the left occipital region. Soon afterward the neck became stiff, so that she had difficulty in turning the head to the left or in bending it backward. In December 1932 she experienced pain in the right shoulder and down the outer side of the right arm. These pains were aggravated by coughing and sneezing. A few months later similar pains were felt in the left arm. In January 1934 she had headache and attacks of nausea, without vomiting. At no time did she notice weakness of the arms or legs. In April 1934 the neck was manipulated for relief of supposed torticollis. On emerging from the anesthesia she noticed that the left leg had become weak and stiff; seven days later the right leg was similarly affected, and movements of the head were further limited. Before manipulation she experienced slight difficulty in starting micturition, but afterward she had retention, followed by incontinence.

Examination revealed that the patient was unable to lie flat in bed because extension of the head caused pain. The head was constantly flexed to the right. There were incontinence and nystagmus. Approximately 3 diopters of papilledema was present in each eye. The motor function in the upper extremities was normal. The tendon reflexes were normal except for diminution of the left triceps jerk. The lower limbs were completely paralyzed. The right leg was held in extension and the left in flexion. The deep reflexes were exaggerated, and there was an extensor plantar response on both sides. Hyperesthesia was present on the outer aspect of both arms as high as the shoulders. All forms of sensation were diminished on the inner aspect of both arms as far down as the elbows and were much diminished in the trunk and lower limbs, up to the level of the second thoracic segment. Postural sense, stereognosis and the results of a compass test were normal in both hands. Postural sense was lost in the toes of both feet. Incontinence of urine was present.

Cervical laminectomy revealed a glioma, both extramedullary and intramedullary. The patient died on October 2; an elongated tumor, partly extramedullary and partly intramedullary, was disclosed extending from the first cervical to the first thoracic segment. It lay posteriorly, and chiefly on the right side of the cord. No cerebral tumor was observed, but there was moderate bilateral hydrocephalus. The tumor did not extend into the foramen magnum, so that the cause of the papilledema in this case is not clear.

WATTS, Washington, D. C.

DEMENTIA PARALYTICA, A SYPHILITIC DISEASE WITH SPECIAL CEREBRAL AND PLURIVISCERAL LOCALIZATION. W. E. MAKAROW, Monatschr. f. Psychiat. u. Neurol. **90**:75 (Nov.) 1934.

According to Makarow, dementia paralytica is a syphilitic disease that tends to involve a number of viscera, as well as the brain. In a study of twenty-six patients, he observed that the heart and aorta showed syphilitic changes in twenty-three instances, the lungs in fifteen and the liver in eleven. Seven patients had involvement of all these organs. Other investigators have demonstrated that early and late forms of syphilis tend to affect the same group of organs but that this type of localization is observed in a larger proportion of cases of dementia paralytica. It is difficult to explain the predilection of the disease for certain viscera. It may be due to differences in the resistance of various organs, to hereditary and acquired predisposing factors and to the virulence of the spirochetes. In dementia paralytica the diffuse degenerative component of the neuropathologic picture is of toxic origin and is probably related to the increasing plurivisceral involvement, with the liver playing an especially important part. The inflammatory component, which tends to be focal, is associated with spirochetal activity locally. Dementia paralytica owes its origin as a nosologic entity to the combined effects of spirochetal activity and toxic disturbances arising from visceral involvement. When this combination reaches a certain level, it leads to diffuse degenerative alterations of the brain, at which moment the syphilitic disease may be called dementia paralytica. Thus, dementia paralytica is not a parasyphilitic or metasyphilitic disorder but represents an advancing syphilitic process developing directly from the early and the late stage of the disease. Inflammatory changes in the pia, which are often present for a long time before degenerative changes occur, may produce an invalid state of the nervous system and may be regarded as a precursor of dementia paralytica. On the other hand, it is possible that degenerative alterations may precede the inflammatory lesions in some instances and prepare the way for the development of the latter lesions. The widely held view that specific treatment is of no benefit in patients with dementia paralytica is undoubtedly related to the conception of the disease as a parasyphilitic or metasyphilitic disorder. According to Makarow, specific treatment leads to definite improvement of the mental symptoms, but this does not last unless malarial therapy is given. He advocates treatment with iodides and mercury or a preparation of bismuth, quinine and iodine, followed by malarial therapy. He recommends this combined therapy as a prophylactic measure in all cases in which visceral or early cerebral involvement is discovered.

ROTHSCHILD, Foxborough, Mass.

ANTERIOR PROLAPSE OF THE INTERVERTEBRAL DISKS. W. HAMMERBECK, Virchows Arch. f. path. Anat. **294**:8, 1934.

In his systematic studies of the vertebral column, Schmorl described a variety of conditions characterized by the presence of cartilaginous nodules in abnormal situations. They were seen most often in the cartilaginous plate or spongy bone of the vertebral body. Larger cartilaginous protrusions of the posterior margin of the disks were also described by Schmorl. These lie beneath the longitudinal posterior common ligament of the spine and protrude into the spinal canal. The formation of cartilage Schmorl held to be secondary to prolapse of the tissue of the nucleus pulposus, brought about by mechanical pressure on the disks. Hammerbeck describes protrusions of the anterior or anterolateral margins of the disks, beneath the anterior common ligament. These are also due to mechanical pressure. They are due to prolapse of nucleus pulposus tissue or, more often, of degenerated tissue of the annulus fibrosus.

SCHULTZ, Evanston, Ill. [ARCH. PATH.]

NECROTIC SPONDYLITIS IN PERSONS WITH TABES. KUND H. KRABBE and P. A. SCHWALBE-HANSEN, Acta psychiat. et neurol. **10**:317, 1935.

The authors report seven cases of tabes with clinical and roentgenographic evidence of osteonecrotic changes in the lumbar vertebrae. They are opposed to the neurotrophic and endocrine theories of the pathogenesis of these changes and support the view of Barré who regarded the necrotizing spondylitis as a result of the syphilitic phlebo-endarteritis. They argue that if these changes were of a neurotrophic nature they should occur also in association with spinal myopathies, chronic diffuse myelitis and tumors of the cord. The syphilitic meningitis observed in tabes, localized about the posterior roots and ganglia, leads to obliterating endarteritis of the spinal arteries in the intervertebral foramina and thus offers a simpler explanation of the necrotic changes in the vertebrae.

YAKOVLEV, Waltham, Mass.

TRANSVERSE ASCENDING MYELITIS. E. BEHR and J. WUITE, Acta psychiat. et neurol. **10**:657, 1935.

Behr and Wuite report two cases of transverse ascending myelitis, with autopsy. A previously healthy boy aged 12 years one day complained of backache, weakness and numbness in the legs and fever. In the course of the next day flaccid paralysis of both lower extremities, with total anesthesia and retention of urine, developed. All deep and superficial reflexes were lost. The spinal fluid was cloudy and yellow; the cell count was increased, and there were many polymorphonuclear leukocytes. The next day the spinal fluid was frankly bloody. Cultures were sterile. The paralysis and anesthesia rapidly progressed upward, involving the trunk and upper extremities. Seven days after the onset the patient died of paralysis of the muscles of respiration. Autopsy revealed hemorrhagic meningomyelitis, with necrotic softening of almost the entire cord. In the case of a man aged 35, the onset, course and symptomatology of the condition were identical with those in the first case, but the condition progressed more slowly. The spinal fluid, at first purulent, later became bloody and purulent. There were many polymorphonuclear leukocytes. The pressure and the protein and sugar contents were increased. With arrest of the acute myelitic process improvement in the spinal fluid picture took place. The patient survived for seven months. There developed severe atrophy of the paralyzed lower extremities, incontinence of urine and feces and decubitus. Autopsy revealed complete necrotic softening of the spinal cord from the fourth dorsal segment down. There was evidence of some degree of vascular organization by sprouting blood vessels from the meninges. In from the third dorsal to the fifth cervical segment distinct reactive gliosis was observed. The necrotic tissue contained blood pigment.

The authors regard their cases as being distinct from cases of Landry's paralysis because of the prominence not only of motor paralysis but of severe sensory disturbances from the outset, with transverse involvement of the spinal cord. They believe that bacterial toxins are probably responsible for the hemorrhagic necrosis of the cord, the spread of the infection occurring by way of the blood vessels and lymphatics.

YAKOVLEV, Waltham, Mass.

Peripheral and Cranial Nerves

THE MALIGNANT TUMORS OF THE PERIPHERAL NERVES A. P. STOUT, Am. J. Cancer **25**:1, 1935.

Two classes of primary malignant tumors develop in the peripheral nerves—those of mesoblastic origin and those derived from neuro-epithelium. The mesoblastic tumors form by far the largest group. They can be subdivided on histologic grounds into the uncommon malignant neurofibroma and the common fibrosarcoma. The malignant neurofibroma reproduces the simple neurofibroma on a large scale, with the development of atypical cell forms. The fibrosarcoma is made up of spindle cells, which are arranged in interlacing bundles, and of collagen fibers, which tend to be wrapped about every cell. The great majority of all these tumors occur in persons suffering with Recklinghausen's disease. The striking clinical features include persistent growth, frequency of reappearance after attempted surgical removal and metastasis (in 20 per cent of the cases of fibrosarcoma). Of tumors reported as belonging to the neuro-epithelial group only three are acceptable. These presented varying histologic features. Four other recorded tumors which may have been primary malignant neuro-epithelial growths are discussed but are rejected for lack of proof. One of these was probably a metastasis from a primary tumor of the lung. Tumors derived from ganglia which happen to be situated within various nerves are not considered primary tumors of the nerves. They are referred to briefly, as one pigmented paraganglioma of the ganglion nodosum situated in the vagus nerve is reported in illustration.

FROM THE AUTHOR'S SUMMARY [Arch. Path.].

NEUROPATHY IN DIABETES: LIPID CONSTITUENTS OF THE NERVES CORRELATED WTH CLINICAL DATA. WILLIAM R. JORDAN and L. O. RANDALL, Arch. Int. Med. **57**:414 (Feb.) 1936.

Samples of nerves removed for biopsy were examined for lipid content. Fifty-two samples were obtained from patients with diabetes and twenty-three from persons who did not have diabetes. The average lipid content was invariably lower for persons with diabetes, the average figures for persons who had diabetes and for those who did not being: for phospholipid, 2.8 per cent and 4.4 per cent, respectively; for cholesterol, 0.9 per cent and 1.5 per cent, and for cerebrosides, 1 per cent and 1.7 per cent. Nerves from the lower part of the leg of patients with diabetes showed greater damage (i. e., lower lipid content) than nerves from the thigh and pelvic levels. The relationship between the severity and controllability of the diabetes, on the one hand, and the damage to the nerve, on the other, was not definite. Previous control of diabetes seemed significant in the neuropathic observations, but because of the difficulty in determining this factor the results are of doubtful value. The duration of the diabetes bore no relation to the damage to the nerves. Age alone did not affect the lipid content of the nerve sections. On the other hand, circulatory efficiency did have some influence, since it was observed that the greater the circulatory defect or the arteriosclerosis the lower the lipid content. Even clinical manifestations of neuritis were not closely correlated with neuropathic changes, since in many instances these changes exceeded the clinical manifestations of involvement of the nerves.

DAVIDSON, Newark, N. J.

PAROXYSMAL NEURALGIC TIC AS A SEQUEL OF TRIGEMINAL NEURITIS. WILFRED HARRIS, Brit. M. J. **1**:1112 (June 1) 1935.

Harris proposes that paroxysmal neuralgias which are not due to any gross lesion or irritation of the fifth or ninth nerve ought be designated, respectively, trigeminal and glossopharyngeal tic.

Eight hundred and fifty-three cases of the former were seen in private practice. Three of these appear to belong to a class hitherto undescribed. In each there occurred rapid or sudden onset of complete numbness of one side of the face, including the eye, forehead, lips, jaws and tongue; the anesthesia was so complete that the lip or cheek was liable to be bitten. The numbness lasted from a few weeks to four years, but in each case it subsided completely. The disappearance of the numbness was succeeded by spasms of paroxysmal trigeminal neuralgia, which yielded to the injection of alcohol.

Notation is made that trigeminal tic occurs with some degree of frequency in chronic cases of spastic paraplegia. Three typical cases of disseminated sclerosis are described in which trigeminal anesthesia was present for a few weeks.

BECK, Buffalo.

NON-ALCOHOLIC POLYNEURITIS ASSOCIATED WITH THE KORSAKOW SYNDROME. LOUIS MINSKI, J. Neurol. & Psychopath. **16**:219 (Jan.) 1936.

Polyneuritis associated with Korsakoff's syndrome may be produced by etiologic agents other than alcohol. Four such cases presenting the typical clinical picture are reported. In case 1 the condition was associated with toxemia of pregnancy and postpuerperal septicemia, followed by severe gastro-enteritis with profuse diarrhea. In case 2 there was a condition of the upper respiratory tract, followed by a gastro-intestinal infection with Bacillus aertrycke that resulted in profuse diarrhea. In cases 3 and 4 there were no obvious etiologic factors except a history of an earlier attack of diabetes in the first case and of diphtheritic polyneuritis during childhood in the second. Opinions in the literature are divided as to the importance of the causative rôle of toxemia and avitaminosis (vitamin B complex and vitamin A) in the production of polyneuritis. Minski concludes, on the basis of the first two cases primarily, that toxic and deficiency factors must both be considered in the etiology.

N. MALAMUD, Ann Arbor, Mich.

ZONA AND ANTISYPHILITIC CHEMOTHERAPY. GREGOIRE I. ODOBESCO and H. VASILESCO, Encéphale **30**:649, 1935.

Four cases of herpes zoster following antisyphilitic treatment are reported. Three occurred in patients with dementia paralytica and one in a patient with schizophrenia in whom syphilis was discovered in a routine Wassermann test. Medication consisted of the use of neoarsphenamine and bismuth and, in one case, intraspinal injections of mercury bichloride. Odobesco and Vasilesco believe that the zona is not of syphilitic etiology but is an ectodermosis which requires a peculiar allergy for its appearance. Allergic syphilis may, by some sort of hetero-allergy, call forth the zosterian eruption. From the fact that in the cases reported the eruption followed antisyphilitic treatment, it is concluded that treatment is capable of transforming anallergic dementia paralytica or parasyphilis into allergic syphilis, in the same manner in which malaria therapy is thought to accomplish this transformation. Incidentally, in one case a varicelliform eruption appeared after subsidence of the herpes. To the authors this is an argument against the thesis that zona and varicella have a common etiology, since the patient was not immunized against varicella by the preceding attack of zona.

LIBER, New York.

PROGRESSIVE HYPERTROPHIC FAMILIAL POLYNEURITIS: FORME FRUSTE OF ADULTS. J. DE BUSSCHER and LUDO VAN BOGAERT, J. belge de neurol. et de psychiat. **35**:152 (March) 1935.

The authors report a study of progressive hypertrophic familial polyneuritis in two adults in one family, a brother and sister; in addition, the patient in another

case which was not studied is said to have died of a similar disease at the age of 41 years. The first symptoms noted were gastro-intestinal; in one case a duodenal ulcer was diagnosed roentgenographically. There was cachexia with marked loss of weight, so great that the larger nerve trunks could be palpated easily. There was massive atrophy of the muscular system, beginning in the lower extremities, involving first the legs, resulting in a steppage gait, and eventually the upper extremities, associated with wrist drop. There was marked muscular weakness, with fine tremor of the muscles. Striking vasomotor changes were evidenced by coldness of the extremities and hyperhidrosis, which was increased by emotion or effort. There was marked diminution of all tendon reflexes except the patellar; no pathologic reflexes were noted. In no case were there any significant laboratory findings. All patients had difficulty in movement; this was presumed to be due to weakness, and there was no intention tremor. There were definite sensory changes in the form of hypesthesia. In all cases there was a history of pain in the extremities. Chronaxia measurements suggested the presence of a neuritic process rather than myopathy. Biopsy of a nerve in one case showed more or less normal myelin; there was an increase in the number of fibroblastic nuclei and of the nuclei of Schwann. Study of the muscles showed simple atrophy of some fasciculi, but most of them retained normal striation. There was no multiplication of the interfascicular nuclei. Three biopsies revealed proliferation of the cells of Schwann and of the perineurium and endoneurium, absence of marked evidence of neuritis and histologic evidence of myopathy.

Differential diagnosis must be made from the distal myopathies, the Charcot-Marie type of muscular atrophy and some forms of amyotrophic lateral sclerosis. In the first two conditions there is absence of sensory changes. The presence of neuritic pains and disorders of sensation are important clinically in distinguishing the syndrome described from that of Charcot-Marie atrophy, particularly when the hypertrophic neuritis manifests itself in an abortive form. The authors assume that disturbance of the cells of Schwann is manifested first and that involvement of the myelin and axonal degeneration do not appear until later.

WAGGONER, Ann Arbor, Mich.

PRESENCE OF PREERUPTIVE PRIMITIVE ADENITIS IN ASSOCIATION WITH SHINGLES. JULES FRANÇOIS, J. belge de neurol. et de psychiat. **35**:209 (April) 1935.

The lymphatic system is said to be almost invariably involved in cases of shingles. François distinguishes primitive adenitis, which is moderate and without tendency to suppuration, from secondary adenitis, which is more rare and tends toward suppuration. It is suggested that the adenitis is caused by the virus which produces the shingles. He presents two cases of ophthalmic zoster in which the preauricular adenopathy preceded the cutaneous eruption by at least three days. In neither case was severe pain associated with the disease. François found only two similar cases reported in the literature and believes that these, with his own, help to confirm, if not to establish, that there exists in herpes a preeruptive adenitis, which is caused directly by the herpes virus. He assumes that this acts simultaneously but independently on the nervous system to produce cutaneous trophism.

WAGGONER, Ann Arbor, Mich.

A GROUP OF DISEASES COMBINING INVOLVEMENT OF THE BRAIN STEM WITH LESIONS OF THE PERIPHERAL CRANIAL NERVES. ERWIN STENGEL, Deutsche Ztschr. f. Nervenh. **137**:221, 1935.

Stengel reports five cases in which the symptomatology pointed to a combination of neuritis of the peripheral cranial nerves and a disturbance of the central nervous system, and one case in which both facial nerves and the vagus nerve were involved. In the first five cases the facial nerve was frequently involved. The central lesion in these cases was localized in the brain stem, mainly in the medulla and in the tegmentum. In some, the central lesion was in the midbrain.

In none of the cases did the symptoms point to spinal involvement. In some cases the spinal fluid showed either an increase in the number of cells or an increase in albumin content. Stengel can assign no causative factor to account for these disturbances. The history in some cases suggested an inflammatory origin. None of the patients showed an increase in temperature. However, fever may have been present during the earlier stage of the disease. Furthermore, an increase in the cell count of the spinal fluid may have been present during the acute stage of the disease. The course of the disease leads Stengel to consider the condition as an inflammatory one involving the central nervous system as well as the peripheral cranial nerves. He therefore speaks of these cases as instances of neuro-encephalitis due to an unknown virus with affinity for parts of the brain stem as well as for peripheral cranial nerves.

Stengel raises the question whether some cases in which involvement was limited to the peripheral cranial nerves or exclusively to the brain stem might not bear a relationship to his cases of neuro-encephalitis, with the difference that in such cases the disease involves only one of the two parts, either the peripheral or the central part, of the nervous system. As a possibility of such an abortive type, he refers to his sixth reported case, in which there was paralysis of the facial nerves and involvement of the vagus nerve. He also suggests the possibility that some of the cases of polyneuritis of the cranial nerves reported by Frankl-Hochwart may belong in this group of cases of neuro-encephalitis. Pollak has noted that in cases of paralysis of the facial nerve of the rheumatic type the spinal fluid occasionally has been found to be abnormal. Polyneuritides with and without the combination of encephalitis were observed during the epidemic of encephalitis lethargica and were referred to as neuritic forms of encephalitis lethargica (Economo).

BERNIS, Rochester, N. Y.

Muscular System

MYASTHENIA GRAVIS: A STUDY OF POSTMORTEM OBSERVATIONS, INCLUDING THE DEMONSTRATION OF GRAM-POSITIVE BACTERIA (STREPTOCOCCI) IN AND BETWEEN THE MUSCLE FIBERS. HUGH R. BUTT, Arch. Path. **21**:27 (Jan.) 1936.

Necropsy was performed in a case of myasthenia gravis shortly after a similar examination had been made in a case of dermatomyositis, and microscopic study of the muscles in the two cases revealed certain resemblances. The collections of lymphocytes in the muscles in both cases suggested a chronic infection. The inference was that the cause of myasthenia gravis is an infection which becomes localized in the muscles in a manner similar to the localization of rheumatism in joints and that since the lesions in cases of myasthenia gravis, scleroderma and dermatomyositis often present similar pictures, they may all be related to a common type of infection, with different localizing properties. This observation led to the study of the pathologic changes in seven cases of myasthenia gravis in which necropsy had been performed.

Collections of lymphocytes were observed in all but two of the seven cases. In all cases there was a form of degeneration in some sections of muscle. A thymoma was observed in two cases. Gram-positive diplococci and ovoid cocci, which sometimes resembled bacillary forms, were noted within or between the muscle fibers in some sections of muscle in all seven cases of myasthenia gravis. In seven cases used as controls no organisms could be demonstrated in these positions. The possibility of artefact or contamination was excluded. The fact that gram-positive organisms were observed in the muscles of all seven patients with myasthenia gravis and were not seen in the muscles of a similar number of subjects used as a control suggests that these bacteria may be the origin of a toxin which produces the characteristic fatigability in this disease.

WINKELMAN, Philadelphia.

THE CHOLINE ESTERASE CONTENT OF BLOOD IN MYASTHENIA GRAVIS. EDGAR STEDMAN, J. Physiol. **84**:56P (July 24) 1935.

Temporary relief of the symptoms of myasthenia gravis by the administration of the dimethylcarbamic ester of 3-hydroxyphenyl trimethylammonium methylsulfate (prostigmin) has led to the suggestion that this disease is due to abnormalities in the mechanism for the liberation or destruction of acetylcholine. As this drug is a member of a large group which possess the property of inhibiting the activity of choline esterase, this suggestion appears to be justified. Stedman determined the choline esterase content of defibrinated blood from a number of patients suffering from myasthenia gravis, as well as from several normal persons. The values obtained for the former group exhibit a tendency to be low, as compared with the results for normal subjects. This is due largely to the low content of the serum, the corpuscles containing approximately normal amounts of the enzyme. It is not at present certain whether any significance can be attached to these low values. If one assumes that the serum content of choline esterase is a measure of its concentration in the tissues, it is clear that myasthenia gravis is not due to excessive destruction of acetylcholine by the enzyme in question.

ALPERS, Philadelphia.

MYOTONIC DYSTROPHY. ERICH LUKOWSKI, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:147 (Oct.) 1935.

Two typical cases of myotonic dystrophy are described completely by Lukowski. The dystrophy is usually more marked than the myotonia. There was a positive family history in both instances. In one case a Chvostek sign was elicited, which is usually present in about one fourth of the cases. The phosphorus and calcium contents of the blood were normal. In one case there was an enlarged thyroid. Electrocardiograms and roentgenograms of the heart revealed nothing abnormal. An increase in lactic acid was found in the venous blood in one case. The sugar content was high during fasting in both instances, and the sugar tolerance curve was abnormal. Both patients were mentally retarded. Large doses of atropine and the application of an Esmarch bandage and cold caused the myotonia to disappear temporarily. No definite conclusion is given regarding the nature of this malady.

SAVITSKY, New York.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

Regular Meeting, Oct. 9, 1936

DR. FREDERICK H. ALLEN, M.D., *Presiding*

BABCOCK TEST FOR MENTAL DETERIORATION. DR. R. S. BOOKHAMMER and MISS BEATRICE RUBIN (by invitation).

Mental deterioration, according to Babcock, is impairment of mental functioning with no implications as to possible causes, whether physiogenic or psychogenic, and as to whether the condition is permanent or temporary. Impairment of mental functioning is manifested in patients by difficulties in forming new associations, making correct associations, retaining recent memories and fixating attention. Mental deterioration is encountered as a symptom in many psychoses, principally in those in which there is widespread organic disease of the brain, namely, dementia paralytica, arteriosclerosis, alcoholism and epilepsy. Ordinary psychiatric methods do not allow for the accurate determination of the previous mental level, and it is difficult to differentiate between mental deficiency and mental deterioration as the result of the disease process.

Recognizing the need for a yardstick by which to measure deterioration, Babcock devised a series of tests which can be applied readily and which lead to the expression of mental deterioration in terms of an efficiency index. She measures mental deterioration in terms of mental efficiency. The subject-matter of the tests is such that the persons tested are able to comprehend the questions unless the inability to do so results from the deterioration which the test is aiming to find. Mental efficiency is determined by giving the subject a series of 20 tests involving memory, motor control, speed of response and the abilities to fixate attention and form new associations.

In order to determine the degree of deterioration, the final score of this test must be compared with the subject's norm for his mental level. The original mental level of the patient is difficult to obtain by the ordinary tests for the measurement of intelligence. The mere scattering of responses over many year levels is often an indication of deterioration, so that the formal intelligence test is valueless to measure the mental level of a person before deterioration set in. A vocabulary test is thought to be the only means by which the index of a deteriorated person's original mental level can be determined.

The Terman vocabulary test is given to determine the subject's mental level. The mental level having been arrived at, one is able to compare it with the score made in the Babcock test. The difference between the final score and the norm established for the subject's mental level is called "the deficiency index." The efficiency index is the numerical expression of a person's mental efficiency, or the efficiency of his mental functioning.

The examination has been shown to be a valid indication of mental deterioration, as persons nearest the norm are considered more able to adjust than persons below the norm. An efficiency index of —1 is considered within normal possibilities, though below the average normal efficiency. An efficiency index below —3.5 is probably a pathologic sign.

We have used this method in measuring deterioration in cases of dementia paralytica and have found it useful in the quantitative determination of mental functioning. We believe that it is useful in enabling one to distinguish between mental deficiency and mental deterioration.

DISCUSSION

DR. ARTHUR P. NOYES, Howard, R. I.: I have had no personal experience with the Babcock test for mental deterioration. Any expression of opinion must

therefore be a matter of impression. My conception of deterioration is not entirely in agreement with that of Babcock. She refers to deterioration as being temporary at times. This implies that the process may be reversible. To me deterioration implies a process that is not reversible. I have come to think of it as a permanent loss in the mental life, largely in the part which is spoken of as the intellectual sphere. To be sure, in dementia paralytica there may at times be an apparent deterioration which is temporary. When the patient with dementia paralytica first comes to the attention of the physician, he not rarely shows considerable impairment of intellectual function, due presumably to exudative processes rather than to actual destruction of neurons. It may be assumed that in such cases the exudate is absorbed and that with this absorption there may be considerable restoration of intellectual function. In such cases there may be an apparent deterioration which is temporary.

I suppose most have come to look on the injury to the mental life of the patient with schizophrenia as disorganization of personality rather than deterioration in a limited sense. A frequent manifestation of this disorganization is a disturbance in associations and the stream of thought. As all know, the patient with schizophrenia often gives casual replies to questions. Doubtless in many instances, he gives such casual answers to interrogations when he is given any formal psychologic test. I wonder whether these casual replies do not indicate a desire on his part not to be disturbed in his autistic life rather than a true deterioration and whether they are not somewhat in the nature of a defensive and evasive reaction rather than an actual impairment of the mental functions which are ordinarily classified as intellectual. I wonder, too, whether Babcock has found that this apparent deterioration in the patient with schizophrenia is consistently sustained. I think all have had the experience that the attention of the patient with schizophrenia, and therefore the extent to which his replies are casual, may vary from time to time, that when he particularly dislikes to be disturbed the replies are more casual and that when his attention is more easily concentrated his answers are more in accord with the level of his former intellectual functioning. Perhaps, in part, such experiences have led Babcock to consider as deterioration a temporary disturbance in mental functioning of this type. As I said in the beginning, however, these thoughts are mere impressions and are not based on practical experience with the test.

DR. FREDERICK H. ALLEN: One of the points brought out by Dr. Noyes seems to me important. To call this test a measure of mental deterioration is in itself misleading, for the word "deterioration" should apply only to changes which have a degree of permanency. This test seems to be a measure of fluctuation more than of deterioration, and to that extent it is valuable. It could then be used as a test for mental deterioration in cases in which there is indicated a downward trend through varying stages of the psychosis.

In giving this test, the time element is also made an important condition. This factor makes the test still more debatable as a real measure of deterioration. For example, in the ordinary case of retarded depression the correct response may come, but it comes slowly. Certainly, one would speak of this not as an indication of deterioration but only as a result of the degree of retardation at the time the test is given.

DR. J. C. YASKIN: I wish to ask Miss Rubin how she avoids the problem of failure of attention in some cases, especially in those of the catatonic stage, in which attention is almost nil?

MISS B. RUBIN: I have not tested patients who were so demented that I was not able to secure their attention or who exhibited catatonia. Of course, most of the responses are timed. The length of time the patient takes to answer helps to determine the grade he receives for the test.

DR. R. S. BOOKHAMMER: We purposely avoided the use of the Babcock test in cases of schizophrenia. Such disorganization as is shown in schizophrenia is probably not deterioration. The test is of value in the organic psychoses. Perhaps

the term deterioration is not a proper one to use. Neither is the term dementia. I wonder what term one should apply to describe the mental state of a patient who comes to the hospital with considerable impairment of all mental faculties and leaves improved after treatment. This is a reversible process in many instances. Shall one call patients who do not improve deteriorated? Shall one say of those who do improve that they had mental inefficiency? If one uses the word deterioration as Babcock does, meaning impairment of mental functioning, with no implications as to possible causes or as to whether the condition is permanent or temporary, it would seem a satisfactory descriptive term.

ENDOCRINE STUDIES IN CASES OF HOMOSEXUALITY. DR. KENNETH E. APPEL and DR. JAMES A. FLAHERTY.

Utilizing the recently developed methods of assay of "sex hormones," we have combined endocrinologic studies with psychiatric investigation in cases of psychosexual disturbances. Six cases studied in this manner are described in a preliminary report. The psychologic condition was thoroughly considered, and determinations of the androgen and the estrogen content of the urine were made concurrently. Androgen was evaluated quantitatively by the McCahey-Hansen modification of Koch's technic. The method of Frank and Goldberger was employed in determinations of the estrogenic substance, and adsorption with benzoic acid was used for estimation of the gonadotropic principle. Capons and immature and castrated mice were employed. An aggressive, mannish, homosexual woman showed a relatively high titer of androgen, with normal excretion of estrogen. A second woman, who was psychically and constitutionally almost identical with the first, excreted normal amounts of both hormones. Two overt homosexual males were studied; one had a normal quantitative excretion, while the other showed a definite depression, in the output of androgen. These findings may be compared with those of Clifford Wright, who found a consistent inversion of the ratio of the "sex hormones" in 9 cases. We could not confirm these results in 4 cases, in which both sex hormones were assayed. Conservatism is urged in the interpretation of endocrine findings in cases of homosexuality; information regarding normal persons used as controls is meager, and investigations in this new field are tentative. Factors unrelated to homosexuality may reasonably cause wide variations in the excretion of "sex hormones" such as diet, disease and altered metabolism.

DISCUSSION

DR. FRANKLIN L. PAYNE: The modern conception of female endocrine function can be stated as follows: Experimental evidence suggests a neurogenic control of the function of the anterior lobe of the pituitary from a center in the hypothalamic area. Among the numerous products of the anterior lobe is the gonadotropic hormone, which stimulates ovarian function. This hormone is probably not sex specific. It is constantly present in the blood and urine, in quantities that are too small for practical demonstration. Because of the instability and difficulties in extraction of this hormone, normal figures have not yet been established, and the results of quantitative determinations made as a routine are usually not dependable.

In response to stimulation by the gonadotropic hormone, the ovaries secrete two hormones: estrogen (the "female sex" or "ovarian" hormone) and progestin. The latter has never been demonstrated in the human blood or urine. Estrogenic substance is constantly present in the body fluids, in quantities which vary with the different stages of the menstrual cycle. Normal figures for the blood and urine contents of this secretion have been definitely established, and such gynecological conditions as functional uterine hemorrhage, oligomenorrhea and amenorrhea present more or less characteristic alterations from the normal, which are recognized by quantitative hormone analysis. For such quantitative determination of the urinary excretion, twenty-four hour specimens are essential, and the results should be expressed in terms of animal units per twenty-four hour output. Because of the quantitative variations during the menstrual cycle, a single speci-

men is not sufficient. It is better to analyze several specimens which are collected at regular intervals throughout a month. In the studies on the female homosexual subjects which Dr. Appel reported, one would not have been surprised to find deficiency in the "ovarian" hormone, but such was not the case.

Male homosexual persons in some instances have been found to excrete large quantities of estrogen. We found no such case in this small series. The presence of estrogen in male urine may be of dietary origin, as Frank and others have shown that many vegetables contain small quantities of this substance. To assume the secretion of estrogen by a male, one must presuppose the presence of tissue which is characteristically female or, as Frank said, "some hidden female biologic quality." The primordial follicles of the ovary and the seminiferous tubules of the testes arise from the same tissue. The occasional development of a tumor containing testicle-like elements in the female is recognized, but so far as I know, a tumor containing ovary-like elements has never been reported in a male. While women with a tumor containing testicle-like elements characteristically become defeminized, homosexual tendencies have not been recognized in any case.

The endocrine approach to homosexuality is new and interesting. The absence of significant findings in this small series of cases should not discourage further studies along these lines.

DR. J. F. MCCAHEY: The short time allowed for discussion will not permit an adequate description of the method of extraction of androgen from the urine. Capons are used as test animals; slides show the head furnishings of a capon, the same bird after injection of a potent extract which has caused growth of the comb and the same bird at a later date, when the comb has regressed.

Androgen, which is also called "male sex" hormone, is apparently a normal constituent of the urine of women. There is a biologic explanation for this, as the medulla of the ovary contains cells which are analogous to those of the testis. In barnyard fowl these cells under certain circumstances may develop into tubular systems with the formation of spermatozoa, and the endocrine function of this testis-like organ may be sufficiently active to change the appearance of the bird from that of a hen to that of a rooster. In women these medullary cells are rudimentary.

In the male there are no cells analogous to those of the cortex of the ovary. There is then no biologic explanation for the presence of estrogen ("female sex" hormone) in the urine of men. Dr. Payne has stated that its presence may be accounted for by the fact that this hormone is found in certain articles of food and may pass unchanged through the system and be eliminated in the urine. Koch and others have found estrogen in the testes of certain species of animals. Many investigators reported the finding of estrogen in the urine of males. The significance of such studies would be enhanced by additional information relative to the biologic factors involved.

DR. FREDERICK ALLEN: Were there no observable evidences of deviations in the physical constitution?

DR. K. E. APPEL: I cannot answer that from the point of view of anthropologic measurements. Briefly, one would say that one of the men had a boyish physique, with broad hips. The other had delicate muscles but was large of bone. I have not tried injections of androgen or estrogen in therapy, for I wished to be sure of the endocrinologic status. I wished to discuss the problem with men working in this field before plunging into therapy. I have worked with these homosexual patients from the psychotherapeutic side, and the delusions and anxiety have improved greatly. They still remain, however, actively homosexual, though to a less degree; i. e., the activity is less frequent and less urgent.

SYMPATHOMIMETIC AMINES. DR. WILLIAM L. LONG.

There is a correlation between chemical structure and the ability of a substance to stimulate postganglionic fibers of the sympathetic nerves, as measured by pressor effects. With two carbon atoms and a nitrogen atom in the side-chain of

a ring, pressor effects can be obtained. By lengthening the side-chain to three carbon atoms, oral activity is conferred. Increase in the number of hydroxyl groups in the ring or side-chain decreases the stability and duration of action. For instance, epinephrine, with three hydroxyl groups, has a transitory action; ephedrine, with one hydroxyl group, is longer in action, and phenylisopropylamine (benzedrine), with no hydroxyl group, is still longer. The toxicity decreases with the addition of hydroxyl groups.

Pharmacologically, the amines differ among themselves, although all stimulate the sympathetic nerves. Ephedrine relaxes the bronchi; benzedrine also does this, but not as well as ephedrine. Benzedrine causes better relaxation of the intestine, without loss of motility. Neither drug seems to raise the blood pressure in shock.

In addition, benzedrine has a marked stimulating effect on the central nervous system, abolishing fatigue and causing insomnia, restlessness, euphoria, tachycardia, sweating and sometimes headache. It is of great value in preventing attacks of narcolepsy. It is of use in conjunction with stramonium in treatment for the lethargic type of encephalitis. It is used to relax spasm in the intestine, in order to obtain better roentgenograms. Its influence on mood is remarkable, and it is used in combating depression.

The addition of a hydroxyl group to the ring (parahydroxylphenylisopropylamine) seems to abolish most of the central stimulating effects without interfering with the peripheral effects. For this reason, this substance may become of use in medicine, when the central stimulating effects of benzedrine are not desired.

DISCUSSION

DR. WINIFRED STEWART: I am indebted to Dr. Long not only for calling my attention to the therapeutic value of benzedrine sulfate but for his clear discussion of the sympathomimetic amines.

Dr. P. L. Davis and I are studying the therapeutic action of benzedrine sulfate on the parkinsonian syndrome of chronic epidemic encephalitis. We have approximately 90 patients under observation in the wards and the outpatient department of the Philadelphia General Hospital; while our study is not yet completed, we believe that thus far our results are of sufficient interest to warrant a preliminary report.

Owing to the fact that the majority of patients available for this study were already receiving either scopolamine or stramonium for relief of symptoms and that previous experience had proved that it is almost impossible to withdraw these drugs without causing the patients discomfort, we decided to continue the previous medication and study the effect of benzedrine sulfate with regard to its synergic action with scopolamine hydrobromide and stramonium as well as its effect on the patients in whom these drugs were not being used. Of our series of patients, 60 per cent are receiving scopolamine hydrobromide or stramonium.

At the beginning of the experiment an estimate was made of the physical status of each patient while receiving a constant dose of the medicament to which he had become accustomed. Benzedrine sulfate was then prescribed in addition to the standard therapy. Any alteration in the physical status of the patient can therefore be ascribed either to the action of the benzedrine sulfate itself or to its synergic action with scopolamine or stramonium.

Thus far, 85 per cent of the patients have shown definite improvement. This improvement consists in a decrease in fatigability and an increase in mental alertness and energy. Extrapyramidal rigidity has been reduced in many cases, and tremor is not as severe as before the treatment was begun. Several patients have reported reduction in the frequency and severity of oculogyric crises. On the whole, the majority of patients are more alert and energetic and less absorbed in their physical handicap than formerly. Many of them have become more self-reliant, cheerful and interested in problems other than those directly concerned with their disability.

The effect on the blood pressure of patients with postencephalitic parkinsonism is also of interest. We arbitrarily chose a systolic pressure of 120 mm. of mercury to determine the dosage of this drug; patients with a systolic pressure of 120 mm.

of mercury or over were given 40 mg. of the drug a day, and those with a systolic pressure of less than 120 mm. received 60 mg. a day. In about half the patients some alteration in blood pressure was observed. There was an increase in 18 per cent of the patients, a decrease in 18 per cent and an increase of about two weeks' duration, with a subsequent fall to the normal level for the subject, in 15 per cent. In only 8 patients was the rise of blood pressure of sufficient magnitude to require a reduction of the dose.

The unfavorable symptoms produced by this drug are: profuse sweating, when large doses are given; insomnia, when the drug is administered late in the day, and restlessness in some cases in which hyperactivity is a feature of the disease. However, thus far the beneficial results of this drug outweigh the untoward effects sufficiently to lead us to believe that benzedrine sulfate will be accepted as a valuable aid in the treatment for postencephalitic parkinsonism.

DR. P. L. DAVIS: I have been working with Dr. Stewart at the Philadelphia General Hospital on the use of benzedrine sulfate in cases of postencephalitic parkinsonism. Certain observations made me think it would be useful in other conditions. It has been shown that benzedrine has a prolonged vasopressor action. Its action is more sustained and prolonged and is dissipated more slowly than other well known sympathomimetic drugs. It has been estimated by various observers that the action of benzedrine is three or more times as prolonged than that of ephedrine. In a preliminary report, Dr. Ralph Tovell showed that in all but 3 of 31 cases of spinal anesthesia, benzedrine was effective either in preventing further fall in or increasing the blood pressure. I was interested in hearing Dr. Long say he hoped benzedrine would be tried in treatment for orthostatic hypotension. I have had 2 patients with orthostatic hypotension under observation to whom I have given benzedrine, with gratifying results. Recently, Chew, Allen and Barker reviewed the literature on orthostatic hypotension and added 6 cases. They used 50 mg. of ephedrine every two hours, starting one-half hour before arising and continuing until 6 p. m. With my 2 patients I used 20 mg. of benzedrine, one-half hour before arising; 5 mg., at 11 a. m., and 10 mg., at 1:30 p. m. This method seemed to maintain them in comfort. Ordinarily, they complained of syncope, spells of unconsciousness, dimness of vision, sweating and weakness when they stood. I did not notice a marked rise in the readings of the blood pressure when the patient was recumbent, but when he assumed the erect posture, the blood pressure, although it fell as it had before the drug was given, did not fall to a level which previously had given rise to symptoms.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

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ABRAHAM A. BRILL, M.D., *Chairman*

POIKILOTHERMIA, WITH HYPOTHALAMIC LESIONS: A CLINICOPATHOLOGIC STUDY. DR. CHARLES DAVISON and DR. EMANUEL D. FRIEDMAN.

This article will be published in full in a later issue of the ARCHIVES.

EXPERIMENTS WITH QUININE AND PROSTIGMIN IN TREATMENT OF MYOTONIA AND MYASTHENIA. DR. FOSTER KENNEDY and DR. ALEXANDER WOLF (by invitation).

This article was published in the January 1937 issue of the ARCHIVES, page 68.

DISCUSSION

DR. FOSTER KENNEDY: Since our original case, we have had 8 others, in all of which exactly the same results were shown with regard to quinine. Should one

not be less inhibited in thought and action when confronted with disease the pathologic nature of which is not known? If a disease has no known remedy, need one therefore not try empirically to find one? Have not these results in the treatment of myotonia come from recognizing that one did not know but that one had better try to learn? Much thinking is bounded by "the book of words," the experience of others; instead of accepting this implied veto, why not throw an arrow in the air with regard to multiple sclerosis or amyotrophic lateral sclerosis, or other morbid states, the pathologic nature of which is obscure and the remedies for which are not known but which might be discovered by the same kind of directed happy chance? Our method was not merely chance. There was a groping theory behind it, but we preferred to have action prove theory. Surely this is sound tactics in a matter of which one knows as little as one knows of medicine.

DR. JAMES RAMSAY HUNT: I am particularly interested in the fact that Dr. Kennedy and Dr. Wolf seem to have shown the essential lesion of myotonia to be one of the muscle or of the myoneural junction. Heretofore it has been thought by many observers to be of central origin, and in confirmation of this view there are forms of myotonia described which are associated with diseases of the central nervous system—the spinal cord and even the brain. This was the position I assumed in my delineation of the static and kinetic systems of motility. In this conception the static system regulated posture, while the kinetic system was in control of movement. Myotonia was regarded as related to the static system, which was represented in both the peripheral and the central nervous system. Isolated cases of syringomyelia have been reported in which there was associated myotonia. Its association with myotonia atrophica, in which the peripheral neuron undergoes atrophy, is known. I think Dr. Davison and others have shown changes in the sympathetic cells of the spinal cord in that disorder. In association with tumor of the prefrontal region Kinnier Wilson has described a perseveration phenomenon, a persistence of the contraction which is similar to myotonia. It occurred under conditions of voluntary activity and not when the muscles were contracted automatically. This suggests that the mechanism is truly of cortical origin.

I am particularly interested in this subject because of the possible relation of myotonia to the sarcoplasm of muscle. Later researches in physiology by Sherrington and others appeared to indicate that postural tonus is not really related to the sarcoplasm. Studies like this, I believe, open a new field for research, and something important may emerge from it. I believe these investigators are deserving of great credit for their courage and pertinacity and the final success they have obtained.

DR. BERNARD SACHS: The subject is one that has fascinated me, particularly during the past month, after a remarkable exhibition given at the meeting of the Harvard Medical School, during the Harvard Tercentenary Celebration. Dr. Ayer presented a patient suffering from myasthenia, who was hardly able to walk, sit up or lift his head. He was given an injection of prostigmin before the audience and taken out of the room. Dr. Ayer continued with his paper, and after fifteen minutes the patient returned, able to walk up and down the room in front of the audience. That demonstration impressed me as indicating a new conception of what paralysis may be and to what it may be due. There has been glib talk for sixty years or more that paralysis is nothing more than interference with the transmission of impulses from the cortex, through the cord to the muscle. I wonder whether this work may not lead to a complete revision of the entire conception of what paralysis really is and to what it may be due. These investigations are extremely promising, both in a therapeutic sense and in regard to a deeper understanding of the entire function of motion and the question of paralysis.

DR. ISRAEL STRAUSS: I think Dr. Kennedy and Dr. Wolf both know how deeply interested I have been in the work they have done. I feel also—and I think Dr. Kennedy will agree with me in this—that there is no reason for one to be influenced by work of this kind, important as it is, to such an extent as to discard all previous

conceptions of neuromuscular activity. Dr. Kennedy, in his closing remarks, wisely stated, and I fully agree with him, that when one is faced with what seems to be an incurable disease, one ought never to hesitate to keep on trying to cure that disease and to prevent its inception, if possible. Dr. Kennedy, even with the attitude which he assumes and with which I am fully in accord, would not for a moment compare amyotrophic lateral sclerosis with myotonia. Although I agree with him that in the presence of amyotrophic lateral sclerosis one should do everything one can for the patient, it must be recognized that when the disease is diagnosed it has already produced definite destruction of important neuron elements. If by attempting to cure Dr. Kennedy means that one should try in such a case to prevent further development of the disease process, I am heartily in accord with him, but a disease which is so insidious in its onset cannot be cured until one can diagnose it in its early stages and discover the etiologic agent responsible for its development. Dr. Kennedy mentioned multiple sclerosis in the same category with amyotrophic lateral sclerosis. I do not believe they are comparable disease processes. I have thought for a long time—and here, I think, Dr. Kennedy and I part ways—that multiple sclerosis is not an infectious disease. I have maintained that the disease described as "acute multiple sclerosis" is not multiple sclerosis but that multiple sclerosis is a disease which produces a pathologic picture that is familiar and is due to a fundamental change in the body economy, the nature of which is not yet known. However, the fact that the disease has remissions which at times produce a picture of almost perfect health, even though Dr. Kennedy and I may find a few physical signs which make us certain that the patient still has the disease, has led me always to believe that recurrence is not a reproduction due to toxins—and by the way I do not know what a "toxin" is—but that it is a reestablishment in the body of a disturbance in the mechanism, whether chemical or what I do not know, which permits of the reappearance of symptoms. As I have said, this is a different type of disease. The pathologic basis of neither myotonia nor myasthenia is known, I mean, no pathologic change that is characteristic. I have reached a point where the morphologic or the histologic pathologic change represents to me only an end-result of the action of some process injurious to the organism and is not in itself an indication of the nature of the process. Myotonia and myasthenia gravis give no evidence of any destruction of tissue. Therefore, Dr. Kennedy and Dr. Wolf have fortunately chosen a disease which they know must be of functional nature, I mean, a physiologic dysfunction and not one that is characterized by a process of tissue destruction with a pathologic picture, even though the end-result is much more difficult of analysis, cure and prevention.

Dr. Foster Kennedy: Dr. Strauss' remarks provoke thought. One tries to embody one's thoughts in words; and few words really succeed. He contrasted myotonia, a "functional disease with no pathologic changes," and another disease "with a known pathologicomorphologic picture." Now, in this is one not circumscribing one's thoughts and ideas of pathologic processes overmuch by observations with the microscope, just as Jacoby, whom we quoted in our paper, spoke of "no microscopic change in the motor end-plate," as though that were a kind of ultima thule of argument? How many persons in this room know anything important about biochemistry? I think, none. In 1920 I said in my presidential address to this society that neurologists were in a rut, an intellectual rut, that all spoke the same language and said almost the same things and that there should be from time to time as president of this society a physicist or a chemist interested in the notions of neurology. There are such men. They are not always physicians—but no matter. This society ought to have more congress with them, for pathology is no longer a matter only of the microscopic picture. That was the idiom of the last fifty years. In the next fifty years pathology will be expressed in terms of chemistry and electrophysics. Almost by accident, we have had the good fortune, empirically, by character rather than by intellect, by pertinacity rather than by brain, to find in quinine an answer to the treatment of myotonia—an answer which

we do not understand even now that we have found it. Pathology needs Henry Dale or a man of that kind, alert and acute in the knowledge of chemical forces—forces so great one has hardly any conception of them. There is a new wind blowing through medicine, and one must get new ideas running through one's mind as to the varied nature of physiologic and pathologic processes.

PATHOLOGIC CHANGES IN PARKINSONISM (IDIOPATHIC, ARTERIOSCLEROTIC AND POSTENCEPHALITIC), WITH A REPORT OF 15 NECROPSIES. DR. M. NEUSTAEDTER and DR. AMOUR F. LIBER (by invitation).

The regional pathologic change supposedly responsible for all types of parkinsonism, as reported from many reliable sources, is not uniform in character or in its regional selectivity. In all reports prior to 1919 the pathologic changes in the neostriatum and the globus pallidus were regarded by most investigators as chiefly responsible for the syndrome.

The microscopic observations in 15 cases are reported here. Sections of all cortical areas, the basal ganglia, the cerebellum, the brain stem and the cord were stained with Weigert's stain for myelin sheaths, hematoxylin and eosin, cresyl violet and the Nissl and Van Gieson method and with prussian blue, for iron.

Of the 15 cases, 13 were of the postencephalitic type and 2 of the idiopathic type. Cortical alterations consisting of status cribralis or status lacunaris were observed in 4 cases of postencephalitic parkinsonism and of the idiopathic form. Cyto-architectonic disturbances were noted in 2 cases of postencephalitic parkinsonism, and the Betz cells stained poorly. Neuronophagia, cellular atrophy and scattered small glial nodules were observed in 2 cases of the postencephalitic type. Punctate areas of demyelinization in profuse numbers were seen in the subcortical white substance in 4 cases of postencephalitic parkinsonism, and in 1 case of the postencephalitic type in which hemiparesis occurred there was considerable demyelinization in the internal capsule.

The large putaminocaudal cells of the striatum were observed in various degrees of destruction in all cases, without exception. The small cells were affected only slightly in 1 case of the idiopathic type and considerably in 3 cases of the postencephalitic type; they were markedly reduced in number and exhibited considerable neuronophagia; in still another case of the postencephalitic type they stained rather poorly.

The globus pallidus exhibited marked damage in all cases. There was a dearth of cells, and the few remaining cells were shrunken; some were filled with lipoid, and others were swollen, with eccentric nuclei, and contained a darkly granular substance or appeared in narrow band forms, mostly as cell shadows. In addition, there appeared darkly basophilic-staining concretions, loosely scattered throughout the parenchyma and also infiltrating the media of blood vessels and scattered about in droplets along capillaries in the globus pallidus in all but 1 case of the postencephalitic type. These concretions seemed to be fairly limited to this ganglion and were only rarely observed in other parts. With the prussian blue stain they were proved to consist mostly of colloid iron.

The red nucleus was affected in all but case 5, of the postencephalitic type, in which the cells were normal except that they were full of pigment; some stained faintly, and a few were shrunken.

The substantia nigra was severely affected throughout in 12 cases of the postencephalitic type; in case 13 it was affected completely on one side and only partially on the other; it was fairly intact in the 2 cases of the idiopathic type.

The cells of the dentate nucleus were in various stages of degeneration in 12 cases of the postencephalitic type and in 1 case of the idiopathic type. In case 2 only scar tissue remained, in which no cell could be observed. The cortex of the cerebellum was fairly intact in all cases. Here and there, rows of Purkinje cells were missing.

In the medulla the olives were markedly affected in 13 cases and were fairly well preserved in 2 cases of the postencephalitic type.

Changes in the cord consisting of destruction of the anterior horn cells in the cervical region, were observed in case 3, of the postencephalitic type.

The thalamus, the hypothalamus, the locus caeruleus, the substantia innominata of Reichert and, with few exceptions, the mamillary bodies were fairly intact in all cases.

Comment.—While many investigators postulate the destruction of the substantia nigra as responsible for the akinetic-hypertonic syndrome, others observed the destruction of the substantia nigra in cases of residual postencephalitis in which there was no symptom of parkinsonism. On the other hand, there is typical rigidity in the idiopathic and the reported arteriosclerotic type of parkinsonism in which the substantia nigra is intact. It is significant that cases of typical parkinsonism have been reported in which no cerebral pathologic change was present, and in Keschner's case the pathologic alteration was limited to the inferior olives.

Hallervorden, however, observed Alzheimer's fibrillary changes in the cells of the various nuclei in 42 cases of postencephalitic parkinsonism, while with the ordinary staining methods there were in not a few cases apparently normal cells. He interpreted these fibrillary changes as a pathologic state leading eventually to cell degeneration. This might explain the so-called lack of pathologic change in the few cases reported. It might also explain its absence in the globus pallidus in not a few instances of severe parkinsonism.

In the 15 cases in our series the large putaminocaudal cells and the cells of the globus pallidus were uniformly severely damaged. The small cells were slightly affected in 1 case of idiopathic parkinsonism and considerably altered in 3 cases of the postencephalitic type. The nucleus ruber, the dentate nucleus and the olives were also involved in 13 cases. While the substantia nigra was affected in every one of the cases of the postencephalitic type, it was fairly intact in the idiopathic form. This might be explained by the fact that in the postencephalitic phase there is a generalized inflammatory process, in which many parts are simultaneously affected.

However, in the face of such a diverse pathologic picture, it would be futile to attempt definite localization for any one symptom or for the entire syndrome of the various types of Parkinson's disease.

DISCUSSION

DR. JAMES RAMSAY HUNT: Dr. Neustaedter and Dr. Liber add another substantial series of cases to the large number which are already on record. Most of these cases are of what I should call the secondary type of paralysis agitans. They are the result of encephalitis, of diffuse forms of arteriosclerotic change and of senile degeneration, which by their very nature have widespread effects on the brain and other parts of the central nervous system, thus rendering difficult the interpretation of the lesions in relation to function. The authors have properly indicated the difficulties they find in allocating the symptoms of parkinsonism in this great mélange of pathologic changes.

In 1916 I made my first report on the primary atrophy of the efferent system of the corpus striatum (efferent striatal and pallidal systems). This was three years after Kinnier Wilson had published his important work on progressive lenticular degeneration. Before that there were slight indications in pathology that the corpus striatum might be related to such disorders as chorea, athetosis, mobile spasms and even paralysis agitans, but the evidence was confused and uncertain. I had under observation at that time a patient with juvenile paralysis agitans which began as early as the seventh year of life and ran a steadily progressive course for about twenty-five years, before the patient died. In this case I had what appeared to be a progressive system disease, uncomplicated by encephalitis, arteriosclerosis or senile changes. I observed in the corpus striatum a marked loss and destruction of the large motor cellular elements, both in the globus pallidus and in the striatum. These changes affected also the small nucleus basalis, which lies under the pallidum.

I did not observe any essential loss or changes in the cells in other regions of the central nervous system, such as the locus niger, the corpus Luysi or other important central structures. So I postulated that here was a primary system disease which affected only the motor cells of the corpus striatum.

In the corpus striatum the cell content is definite and limited. In the globus pallidus there is only one type of cell: a motor cell which has the same histologic characteristics as the anterior horn cell. It is truly a motor type. In the striatum there are two types of cells: a large cell which is similar to a large motor cell, and numerous closely packed, small cells. In my case, the large cells, both in the striatum and in the globus pallidus, were atrophied, and many were lost. I made numerical counts on sections used as controls and found a loss varying from one half to one sixth of the cellular content, so not only had the large cells the appearance of atrophy but were really gone. The small cells in the striatum were retained.

In further studies of the striatum I observed that in Huntington's chorea the large cells in the striatum and the cells in the pallidum, which are atrophied in paralysis agitans, are preserved, and the degeneration involves only the small cells of the striatum. I therefore formulated the conception that the corpus striatum is an infracortical organ, for the control of automatic associated movements in the extrapyramidal system.

The juvenile type of paralysis agitans is a true system disease, a disease *sui generis,* and is the only type of paralysis agitans which is a primary disease in that sense. It has the same relation to the striopallidal motor system as has primary lateral sclerosis to the pyramidal system. The primary disease is rare, but the system is subject to injury by a diversity of lesions. Therefore, Parkinson's disease is essentially a syndrome. Primary paralysis agitans is as definite as primary lateral sclerosis.

For sixteen years that was the only observation on primary system disease of the corpus striatum, but in 1930 van Bogaert, in a similar case of juvenile paralysis agitans (*Rev. neurol.* **2**:315 [Sept.] 1930) observed essentially the same lesions—degeneration and atrophy of the large cells of the striatum and the cells of the globus pallidus. In addition, however, he noted slight changes in some infrapallidal centers, such as the locus niger and the corpus subthalamicum, which are subordinate centers and related to the striopallidal system. He supported the position that I had taken —that this disease is an abiotrophy.

In 1917, one year after my study of the case of juvenile paralysis agitans, I made pathologic studies in 2 cases of presenile paralysis agitans (*Brain* **40**:58, 1917); there again, I observed atrophy and degeneration of the large cells of the striatum and, to a lesser degree, of the motor cells of the globus pallidus, which supported my previous observations. The condition in these cases, so far as I could determine, was related to an early form of senile degeneration, the kind that Dr. Neustaedter and his collaborator have described as idiopathic, that Jakob has described as cryptogenic and that I had called primary paralysis agitans, in contradistinction to the secondary type of paralysis agitans.

The importance that I laid on these observations, and I have never found it necessary to change that opinion, is that they fixed the corpus striatum as a motor center with a motor projection system which is involved not only as a primary disease but as part of secondary diseases, such as epidemic encephalitis and the manifold vascular lesions. Even the état criblé and the état précriblé of the German writers, as I understand it, are only early forms of vascular change.

There was a period of uncertainty, when Trétiakoff, in 1919, described degeneration of the locus niger in cases of epidemic encephalitis, which later was confirmed and observed in other types of paralysis agitans with few or even no changes in the corpus striatum. At the time some were inclined to accept a lesion of the locus niger as the specific lesion of paralysis agitans. I think it was Spatz who made embryologic and comparative studies of the locus niger and found that the pars reticularis of this center is really only a part of the globus pallidus. It is composed of the same type of cells as the globus pallidus. So, when one speaks of

the locus niger being affected in the akinetic-hypertonic type of paralysis agitans, one is really speaking only of the part of the globus pallidus which has that localization in anatomic studies.

Studies of German observers, except van Bogaert, have never, so far as I have found in the literature, included a case of the primary juvenile type. Their studies were mostly those of regional involvement of the striatum or the globus pallidus, but finally, with respect to the regional syndromes of the corpus striatum, they reached essentially the opinion to which I had come in 1916—that the large cells are related to paralysis agitans and the small cells to chorea. However, I went further with these syndromes and explained, or attempted to explain, all the diverse types of striatal and striopallidal symptomatology as combinations of involvement of these two systems; so the chorea and the paralysis agitans syndrome, in various combinations, account for the whole symptomatology of the corpus striatum. One can readily bring the whole range of syndromes of the corpus striatum under these two system syndromes—the small cells, which are related to chorea, and the large cells of the striatum and the globus pallidus, which are related to paralysis agitans.

Dr. Israel Strauss: My previous discussion was voluntary, provocative though it may have been. The only difficulty with provocative discussions is that I never have the opportunity to answer the objections. This discussion is compulsory. When Dr. Neustaedter began to read his paper, he seemed to apologize for reading a paper on pathologic anatomy, after the preceding remarks to which he had listened. I do not think he need apologize. I think that Dr. Hunt, in his discussion of Dr. Neustaedter's paper, has amply justified the part that pathologic anatomy and the interpretations drawn therefrom have played in the development of neurology. I do not know whether younger men here remember, as do Dr. Sachs and I, the days when the basal ganglia were a *terra incognita*. One did not know what the name meant. It was part of the brain, like the pituitary body, which was a gland about which it was finally learned that it caused certain disturbances, such as acromegaly. But nothing was known about the corpus striatum and the globus pallidus until Hunt—and I say this in his presence—made his studies on that case of juvenile paralysis agitans. The work of Hunt, following that of Kinnier Wilson, it is true, but having a much wider implication, really started knowledge of this part of the brain and its function and dysfunction.

Dr. Neustaedter has shown the results of his studies in a number of cases. It is a pathologic study, but as Dr. Hunt has pointed out, it is a study of diffuse lesions. Of course, Dr. Neustaedter is aware that every part of this system is concerned with the same physiologic function of the brain, whether it is the corpus striatum, the pallidum, the corpus luysi, the substantia nigra, the dentate nucleus or even the inferior olive. In other words, all these structures form a connected system. If one part or another is impaired, there is disturbance of the integrity of the whole system, and if the lesions are sufficiently widely dispersed, the result will be that clinical symptoms arise referable to that dysfunction. That is all, in a way, that this kind of work teaches—a warning not to be localizing in attempts to correlate function and structure in the brain, to realize that the whole central nervous system is an integer which works together and that any part must influence the others. Some parts are predominant in their control of function, but even they may be influenced. Dr. Hunt has shown where certain symptoms have their primary seat, but as he stated, if the system is impaired in other parts, it cannot but impair function, even of the primary seat. I think that is the only lesson to be learned from this careful and exhaustive study. One cannot draw any more definite conclusions as to the function of any one part. One can draw conclusions only as to the function of the whole.

Dr. E. D. Friedman: In all humility I wish to ask Dr. Hunt if he has reviewed his slides in cases of juvenile paralysis agitans to see whether there were lesions in the substantia nigra? The literature today is so full of reports of lesions in this area that it seems to be the region predominantly affected in parkinsonism. I am interested to know whether in these cases any lesions in this part of the pallidonigral system were shown.

Dr. James Ramsay Hunt: In my specimens I observed no changes, but as is known, there are many cases recorded in which no lesions were seen in the locus niger. On the other hand, many cases are recorded, especially of the encephalitic type, in which they were seen. Therefore it is immaterial whether or not I observed them, as it is known that the nigerian syndrome physiologically belongs to the globus pallidus.

Dr. Amour F. Liber: There is no doubt that the substantia nigra is part of the pallidal system, and if lesions are observed in the substantia nigra in any form of parkinsonism, that obviously only supports Dr. Hunt's contention of involvement of the pallidal system. However, I think it is of some importance, albeit secondary, to study the possible regroupings of fiber systems at different levels. While there is no doubt that the substantia nigra must receive fibers from the globus pallidus, it is conceivable that they are grouped in a different way at that level or that all the fibers of the globus pallidus do not go through the substantia nigra. I believe that is probable. In cases, therefore, in which there is a nigral lesion, one expects to find a different type of grouping of the manifestations of the pallidal dysfunction than in cases in which there is no such lesion, just as in the pyramidal system a lesion in the cortex and a lesion at one of the subcortical levels may give different groupings of the signs of essentially cortical dysfunction.

I think the outstanding difference between the so-called idiopathic or cryptogenic type and the postencephalitic type of parkinsonism is that in the idiopathic type there are relatively little hypertonia and relatively more tremor. It is conceivable that a lesion of the pallidal projection fibers at the level of the substantia nigra may contribute more hypertonia and have something to do with the manifestations of less tremor.

A second point concerns the nucleus ruber. In the cases in our series it was almost always involved, and to a considerable extent—partly with atrophy and partly with changes which may be considered degenerative, secondary to section of the afferent fibers. The nucleus ruber is itself considered to be a station along the pallidal projection path. Indeed, to the best of knowledge, the pallidal fibers reach the level of the spinal cord only after a synapse in the nucleus ruber, and the rubrospinal tract is spoken of as the final pathway connecting the pallidal fibers with the lower motor neurons in the spinal cord. Although anatomists have recently expressed doubt of the existence of a collected rubrospinal pathway in man, there is no doubt that it does exist in this form in lower animals, that these fibers, if not present in collected form, do exist in man. This might contribute a slightly different physiognomy to the pallidal dysfunction. I think that in all probability just such differences are manifested by the variability in detail of the parkinsonian syndrome. Undoubtedly, there is a lesion of the pallidal system at some level—practically always at its origin and, in addition in some cases, at way-stations, notably, the nucleus ruber and the substantia nigra.

Unconscious Factors in a Case of Homicide. Dr. Philip R. Lehrman.

The criminal act is regarded as a symptom, and reference is made to the contribution of psychoanalysis that homicide is the dramatic event of a psychologic sequence in which suicidal impulses play a dominant rôle. The schizophrenic murderous act is the preparatory stage for devouring the victim, and as the victim is unconsciously also the representative of the assailant, it is this particular element which gives the quality of suicide to psychotic murder.

I examined a murderer and demonstrated that the external current events which appeared to play a disastrous rôle in precipitating the murder were, in effect, a series of futile efforts on the part of the prisoner to resolve his lifelong difficulty, which was determined by unconscious factors.

DISCUSSION

Dr. Bernard Glueck: The report of this case and the several other reports to which Dr. Lehrman referred, proposing the thesis that murder may be an intent to suicide, just as suicide is murder, may well be a profound and practically

important observation. At any rate, it has led me to reexamine the histories in a number of my cases, which occurred long ago, during the prepsychoanalytic days of my career, and I discovered a great many hints which, if viewed psychoanalytically, would tend to substantiate Dr. Lehrman's thesis. Whether one agrees with him regarding the theoretical elaboration of his case, I think he is to be congratulated on the manner in which he has utilized a rather commonplace experience in psychiatric practice, namely, certification in a criminal case for purposes of research, in the hope of adding to the sum total of knowledge on the subject. It is to be expected that criminals will leave no stone unturned to escape detection and punishment for their deeds, and yet, every once in a while, one encounters a person of the type of this patient, especially, I believe, among murderers, who seems, on the contrary, to leave no stone unturned until he is detected and who appears to experience a distinct relief on being arrested and convicted. There is no doubt that there is a profound masochistic motive in the behavior of these criminals. It explains also, perhaps, some curious manifestations one observes in persons awaiting execution. One would expect that persons who are destined to be electrocuted would demonstrate some sort of adequate reaction to this terrible event. When one observes them, he is constantly surprised at the levity with which they take the entire procedure, at almost a sense of aggrandizement which they exhibit when they march to the electric chair. Indeed, there have been cases on record in which innocent persons managed to involve themselves in a criminal situation and in all sorts of ways endeavored to draw suspicion on themselves and were rescued from the inevitable consequences only by some external intervention. They insisted on being thought guilty and wanted to be punished. One such man was much annoyed by the efforts made in his behalf and complained to me about it. When the fifth reprieve was brought to him, he was distinctly annoyed at this last minute intervention. He was subsequently proved to have been entirely innocent of the murder of which he was accused. All these peculiar phenomena hint at a kind of subjective motivation, which does not fit the objective picture of some criminal acts. I think the thesis that Dr. Lehrman has brought forth may have a practical value, in that one may get into the habit of detecting some of these potential murderers before they actually commit murder if one pays particular attention to some of the frustrations, privations and conflicts which can be discovered in the anamneses of a lifelong struggle which finally culminates in a criminal act, commonly murder.

The case also throws light on the problem of the compulsion neurosis. There may be a great deal more than one is ready to accept at present in the notion that the murderer kills in his victim some unmanageable and inescapable aspect of his own personality. Certainly, that occurs commonly in the dream life of patients. I think this may help to explain also the peculiarly profound depressive episodes that occur in the person with a compulsion neurosis, who, as everybody knows, goes through a lifetime of self-torture and self-punishment, knowing all the time how ridiculous his antics are, while at the same time he has to be constantly busy creating and fostering defenses against his own aggressive impulses. Although Dr. Lehrman's presentation, perhaps because it was too concentrated, may seem far fetched, I think it is precisely that sort of detail, that type of inquiry and of courage to present publicly a clinical history of this sort, which will eventually contribute more to real humanization of criminal procedure than the customary type of report of criminal issues.

DR. A. A. BRILL: With his characteristic wisdom, Dr. Kennedy expressed the hope that in the future this society will have as president an electrician or a biochemist. It seems perhaps a little far fetched to think of such a combination, yet the gap between the points of view expressed here by Dr. Lehrman and Dr. Glueck on the question of homicide and those that are ordinarily entertained by jurists in the criminal courts is just as great.

JUSTICE FREDERIC KERNOCHAN (by invitation): The case of homicide which Dr. Lehrman uses as the basis of his paper, in which he analyzes the unconscious factors leading up to the crime, is not in any way peculiar; that is, the facts are not

different from those in many cases that come before the criminal courts. Here, a man who apparently had no motive deliberately shot one who had been his friend, causing his death—on its face, murder in the first degree. The murderer made no attempt to escape but gave himself up to the authorities almost immediately. The authorities, police, prosecutor and court must have thought that here was a straight case of murder that would be disposed of as a routine, followed by the death penalty or, at least, life imprisonment.

How Dr. Lehrman stepped into the case I do not know, probably because the prisoner, or shall I call him the patient, set up a defense of insanity. That, to my mind, was a proper defense, and if the reasons advanced by the state for the commission of this brutal murder are correct, it would be a major crime on the part of the community to punish the patient either by execution or by imprisonment. Whether or not Dr. Lehrman's conclusions are correct, I cannot say. That is a task for psychiatrists. As for me, I am only too glad to accept them.

I assume, therefore, that this murder had to be, that the murderer was urged to commit it by forces beyond his control. If that is so, punishment for it is of no avail, for it would do the patient no good and punishment would not benefit society, since it would in no way deter others from the commission of a like offense, the circumstances, of course, being the same.

I have said that this murder was not peculiar. It was in a way peculiar, for on its face there was practically no motive or reason for it, and it falls into the class of homicides in which the motive or reasons for such a serious crime are wholly inadequate.

This now brings me to an important question. How can one use the knowledge gained by psychoanalysis and psychiatry—I hope I have used the proper terms—to bring about a proper disposition in a case of this sort.

From the standpoint of the prosecuting authorities, this case was a simple one. It was no task to establish the fact that one man killed another, and the identity of the killer is established beyond any doubt. The problem in this case is how properly to deal with this killer and others in cases similar to this.

The answer to my mind is obvious. There must be a closer relationship between psychiatrists and alienists and those who have to do with the enforcement of the criminal law—judges and prosecutors and especially the public, for their attitude is the greatest force involved in the administration of all laws.

I assume that Dr. Lehrman's introduction into this case brought about a satisfactory disposition; by this I mean that the patient was neither put to death nor imprisoned by the state. I hope he was not set scot-free, for a person of his psychologic make-up must be an element of danger to the community.

How can one bring about this closer relationship between physicians, officials and the public? I know that attempts to this end are being made in various parts of the country. I know that progress has been made and that valuable legislation has been passed narrowing the gap that exists between those who approach these problems in a scientific way and those whose approach is purely legalistic.

There is much to be done in New York. I assume that efforts are being made. Results can be obtained only by a careful study by a group made up of physicians, lawyers, including judges, and selected representatives of the public at large. The personnel of this group should consist of men and women—broad-minded, tolerant, patient and intelligent—persons who can work together without prejudice, one against another, who can be both persuasive and persuadable and who will be willing to give time to this important question. Perhaps such a group cannot be found, either in heaven or out of it, but I think an attempt should be made, and when it is found, much progress can be made.

I wish to ask Dr. Lehrman what the final disposition of this patient was.

DR. PHILIP R. LEHRMAN: In reply to Judge Kernochan's inquiry: In this instance it is to the credit of justice in New York State that a district attorney from a near-by community sought for an unbiased psychiatric opinion of the prisoner. The case did not come to trial, as the prisoner, at a hearing in the judge's chambers, was committed to a hospital for the criminally insane.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 15, 1936

PERCIVAL BAILEY, M.D., *presiding*

HYPOTHALAMIC CONTROL OF REGULATION OF TEMPERATURE IN THE MONKEY. DRS. S. W. RANSON, C. FISHER and W. R. INGRAM.

This article will appear in full in a later issue of the ARCHIVES.

CONSTITUTIONAL DIFFERENCES BETWEEN DETERIORATED AND NONDETERIORATED PATIENTS WITH EPILEPSY: I. STIGMAS OF DEGENERACY. DR. HARRY A. PASKIND AND DR. MEYER BROWN.

This paper was published in full in the November 1936 issue of the ARCHIVES, page 1037.

ESTIMATION OF THE VOLUME OF CIRCULATING BLOOD IN PATIENTS WITH SCHIZOPHRENIA AND OBSERVATIONS ON THE VOLUME OF CIRCULATING BLOOD IN PATIENTS WITH MANIC-DEPRESSIVE PSYCHOSIS, EPILEPSY, INVOLUTIONAL PSYCHOSIS AND MENTAL DEFICIENCY. DR. ISIDORE FINKELMAN AND DR. DANIEL HAFFRON, Elgin, Ill.

The volume of circulating blood was estimated with the dye method in 39 patients with schizophrenia, 15 with manic-depressive psychosis, 6 with epilepsy, 7 with involutional psychosis, 7 with mental deficiency, 2 with a paranoid state, 1 with senile dementia and 1 with psychopathic personality. Estimation of the volume of circulating blood in patients with schizophrenia is part of a systematic program of determining the water balance, capillary permeability, reactions to the antidiuretic hormone of the posterior lobe of the pituitary, heat regulation and oxygen consumption rate in this disorder. We found a low volume of circulating blood in patients with dementia praecox, as compared with that in persons with manic-depressive psychoses, in whom the volume approaches normal values. The patients with schizophrenia had a blood volume per square meter of body surface of 2,609 cc., as compared with 2,973 cc. in manic-depressive patients. The plasma volume in patients with dementia praecox was 1,433 cc. per square meter of body surface, as compared with 1,727 cc. in the manic-depressive patients. The blood volume per kilogram of body weight in a patient with schizophrenia was 78.9 cc. and the plasma volume 43.3 cc., as compared with 87.9 and 50.9 cc., respectively, in patients with manic-depressive psychosis. The percentage of red cells was 45.2 for patients with schizophrenia and 43.5 for those with manic-depressive psychosis. The definite diminution in the volume of circulating blood in patients with dementia praecox is related to disturbances in water metabolism, capillary permeability and vasomotor tonus, secretion of the antidiuretic and vasopressor hormones of the posterior lobe of the pituitary gland and the basal oxygen consumption rate and indirectly to heat regulation. These physiologic processes are regulated by hypothalamic centers. The hypothalamus is also the region of the brain concerned with emotional expression. Thus, physical variations in schizophrenia, of which the diminution in the volume of circulating blood is an example, are probably due to a dysfunction of the hypothalamus, which also determines the continued absence of the physical signs of emotion and the parallel characteristic mental symptoms of emotional indifference in schizophrenia.

The average volume of circulating blood in 6 patients with epilepsy was low. The average blood volume per square meter of body surface was 2,738 cc., and the plasma volume was 1,440 cc. The blood volume per kilogram of body weight was 78.4 cc., and the plasma volume, 41 cc. One of the patients, however, had a blood volume of 4,478 cc. per square meter of body surface and a plasma volume of 3,800 cc. per square meter. This variation indicates that there is not necessarily

a tendency toward a high blood volume or hydration in epilepsy but a disturbance in water balance, or more specifically, in electrolyte balance. A "leakage" of potassium ions through the membranes of the body and brain cells would cause a corresponding change in intracellular water, which would be reflected in variations in blood volume.

The volume of circulating blood in patients with involutional psychosis was lower than that in patients with schizophrenia. The values were similar in all patients with involution psychosis, which would indicate that the disease is a true clinical entity.

There was great variation in blood volume in patients with mental deficiency, but the average was lower than normal.

DISCUSSION

DR. CHESTER DARROW: Were any differences observed among the patients with schizophrenia, particularly between those in the paranoid and those in the hebephrenic group?

DR. J. KASANIN: Dr. Finkelman's conclusions follow careful work, but the histologic work on the hypothalamus did not show that schizophrenia is localized there. I know of only one man who has tried to associate any change with schizophrenia, and that was Kleist. I think one should be particularly careful about drawing conclusions. Conclusions by analogy are the most dangerous. I had an opportunity to see the work at the Worcester State Hospital this summer. There they found that patients consume a great quantity of water and expressed the opinion that schizophrenia is due to water imbalance. After investigation they found that patients with schizophrenia take water in order to purify themselves; this was dependent entirely on a feeling of guilt.

DR. ISIDORE FINKELMAN: In regard to a normal value, I think that the comparison of one psychotic group with another is as valid as that of a psychotic group with a so-called normal group. It also serves as a control for the effects of institutionalization.

In answer to Dr. Darrow: We thought at first that there was a difference between values for the paranoid group and those for the other groups, but as the work progressed we found that this is not the case.

We tested many more patients than those in the cases reported. We excluded many patients because we thought the data was not reliable and included only persons into whose vein we knew that we injected the correct amount of dye. I question the statement that the blood volume can be varied by increasing the water intake. Dr. T. T. Stone and Dr. H. Chor, of the Northwestern University Medical School, were unable to increase the blood volume by increasing the water intake. It seems that the blood volume is more stable than some believe. The excessive intake is immediately taken care of by the bladder and the gastro-intestinal tract and by sweating, and the blood volume is strikingly constant.

As to dehydration, one can decrease the blood volume by excessive sweating, but none of our patients was subjected to this procedure. We did not give the patients used as controls any more water than the patients with schizophrenia, but all were tested under the same conditions. I wish to correct the impression that with every glass of water one drinks the blood volume will increase.

In answer to Dr. Kasanin: I stated distinctly that we are not drawing conclusions from this particular work on blood volume alone. I have published a paper showing that heat regulation is defective (Finkelman, I., and Stephens, W. M.: *J. Neurol. & Psychiat.* **16**:321 [April] 1936). We have data showing changes in gastro-intestinal reactions. I do not know why defective water balance leads to a conclusion of anal fixation—or was it oral fixation—rather than to that of a disturbance in function of the hypothalamus. If one were to follow Dr. Kasanin's method of drawing psychologic conclusions from physical observations, one should conclude that in diabetes insipidus there is a feeling of guilt and an oral fixation because the patient drinks excessive quantities of water.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, Oct. 15, 1936

STANLEY COBB, M.D., *Presiding*

PATHOGENESIS OF MULTIPLE SCLEROSIS. DR. BERNHARD DATTNER (Vienna) by invitation.

Contradictory views concerning the nature of multiple sclerosis and the wide scope of the clinical conception of the disease make it necessary to study the pathogenesis from various aspects. In connection with the tuberculotoxic theory of Gerhartz, I have carried out the test for tuberculosis with the antigen of Kuhn, Witebsky and Klingenstein on 177 patients with various diseases of the central nervous system; some of the tests were repeated a number of times, so that a total of 600 reactions were evaluated. Seventy-one of the patients had multiple sclerosis; of these 68 per cent showed a positive complement-fixation reaction, while of the patients used as controls only 34 per cent showed a positive reaction. The reactions, however, fluctuated in an extreme manner within short intervals of time, without apparent relation to the course of the disease. Beside this, little evidence was found for the presence of a tuberculous process; this, however, does not speak against metatuberculosis.

On the basis of clinical observations, I have studied the function of the intestinal tract of patients with multiple sclerosis and have examined the gastric juice of 90 patients. As controls a like number of patients with epilepsy was studied. In 37 per cent of the patients with multiple sclerosis, the gastric juice was anacid or gave values of under 10 degrees for free hydrochloride acid, as compared with 13 per cent of the patients with epilepsy. This disturbance in the secretion is of great importance and may be compared with that in pernicious anemia and achylic chloranemia, which, according to the newest interpretation, is held to be responsible for the decrease in function in the sphere of the central nervous system. Manifold changes in the blood, in the sense of slight hyperchromic or hypochromic anemia, were also present in the patients suffering with multiple sclerosis. The considerable increase in the blood clotting time of many of the patients with multiple sclerosis is worthy of consideration as the expression of a metabolic disturbance depending on the liver. Finally, I may refer to the similarity in the type and manner of appearance, the clinical course and the symptomatology of multiple sclerosis, funicular myelosis and diseases of the central nervous system due to avitaminosis (beriberi, pellagra and scurvy). It may be possible to differentiate many groups of the diseases now classed under the common name of multiple sclerosis. Of these groups one may possibly be of tuberculotoxic genesis, and another may show avitaminosis as the etiologic factor; however, the list of causes for the appearance of multiple sclerosis is not completed with these few examples. It is also possible that these etiologic factors mutually involve or influence each other.

NATURE OF THE "SILVER CELLS" OCCURRING IN MULTIPLE SCLEROSIS AND OTHER DISEASES. NATHAN BLACKMAN, A.B., Fall River, Mass., and DR. TRACY J. PUTNAM.

This article will be published in full in a later issue of the ARCHIVES.

DISCUSSION OF PAPERS BY DR. DATTNER AND DR. BLACKMAN AND DR. PUTNAM

DR. L. ALEXANDER: The studies which my associates and I made last year on micro-incineration (Alexander, Leo: Cerebral Changes in Gastro-Intestinal Infections with Terminal Cachexia and Their Relation to Physicochemical Properties of the Brain, ARCH. NEUROL. & PSYCHIAT. **34**:235 [July] 1935) and to which Dr. Putnam referred in his paper have given interesting information concerning the mineral structure of the plaques of multiple sclerosis and of the phagocytic

cells observed in them. With a low magnification the plaques stand out as dark, demineralized areas. In early, hyperemic plaques only the engorged blood vessels and the meshes of the glial network are outlined as light, mineral-containing bodies, against the black background of the plaque. The engorged small blood vessels and capillaries, many of which contain early thrombi, show in their adventitial spaces large phagocytic cells which are rich in reddish yellow granules of iron oxide and white granules of calcium. We think that these cells are identical with Steiner's silver cells. Many of these cells, as shown in slides stained as controls contain also lipoid material. The admixture of minerals with lipoids occurs also in Ciaccio's cells in the spleen.

DR. T. J. PUTNAM: There must be a multiple cause for the disease known as multiple sclerosis. We have often wondered about the relation between tuberculosis and multiple sclerosis and are struck by the fact that some persons have both diseases. Autopsies performed on 2 patients in which the diseases coexisted showed that tuberculosis was very active in one, with thrombi in the liver and other organs. An increase both in the number of platelets and in the sedimentation time is recognized in tuberculosis. I feel somewhat more skeptical of the rôle of a deficiency disease. We have studied the gastric juice in many patients and have found it normal in most instances. In 1929 we investigated the question of diet in relation to multiple sclerosis. Dr. Maurice Fremont-Smith and I gave some patients a liver diet high in vitamins, with no beneficial results in the long run.

DR. B. DATTNER: In undertaking my examinations, I chose patients who had been under long observation at the clinic. Later examination of the gastric juice revealed complete anacidity which was resistant to treatment with histamine. I do not believe that in all patients with multiple sclerosis one will find this condition, but one should try to exclude this group.

FURTHER REPORT ON A CASE OF SLEEP LASTING FIVE YEARS, WITH LOSS OF SENSE OF REALITY.

PROF. PIERRE JANET, Paris.

Before commencing the study of a case of pathologic interest, allow me to present the compliments and best wishes of the Société de Neurologie and of the Société Médico-Psychologique of Paris, which have charged me with being their representative. I am happy at having this opportunity to thank the members of this society for their friendly reception and to recall the affection of the French societies for their sister societies in the United States.

The observation which I wish to present is not new. I reported it at the Forty-Seventh Annual Meeting of the American Neurological Society, at Atlantic City, N. J., in June 1921. The observation was summarized in an article (A Case of Sleep Lasting Five Years, with Loss of Sense of Reality, ARCH. NEUROL. & PSYCHIAT. **6**:467 [Nov.] 1921).

I wish this evening to present the later history of this patient, from 1921 to the present. One must allow each worker his own methods of study, and I lay great importance on the continual observation of the same patient through many years. My last book, *"De l'angoisse à l'extase"* (Paris, Félix Alcan, 1926), is based altogether on the continued observation of a single patient to whom I gave the name Madeleine and who presented an interesting religious delusional state with episodes of ecstasy, even with the development of stigmas on the hands and feet.

I shall report a similar prolonged observation of another sleeping patient, whom one may call "The Sleeping Beauty" and who presents symptoms which are perhaps even more complex. I cannot be as precise with regard to the observation of Laetitia as I have been with Madeleine, and, without bringing definite conclusions, I shall limit myself to asking the opinion of the members of this society with respect to this strange pathologic evolution.

To summarize briefly the first part of the observation, which has already been published: The mother of the patient seems to have been almost normal; I have been told of a paternal grandmother who resembled the patient and had red hair,

while the other members of the family have either black or very dark hair. The grandmother was always neurotic; after the age of 60 she was the victim of delusions. The father, always a timid man, as he became old, expressed delusions of persecution, which lasted to his death. Two brothers of the patient are well and are intelligent workers.

At about the age of 7 or 8 years, the patient had a severe fall on the head, which was followed by loss of consciousness and indisposition for several days. The relation of injuries of the head of this sort to later nervous troubles is always interesting. At the beginning of puberty, which was difficult and late, the patient had episodes of nocturnal somnambulism. She began to present the periods of asthenia which on my first visit to Boston, in 1904, I reported as a "crisis of psycholepsy which caused for several minutes loss of the feeling of reality and the feeling of acting in a dream" (Boston M. & S. J. **152**:93 [Jan.] 1905). I need not describe the indigestion and the attacks of constipation and mucomembranous colitis, which are so frequent in all neurotic patients. From the age of 17 the crises of psycholepsy with the feeling of loss of reality were accompanied by feelings of heaviness and immobility.

Similar attacks in Madeleine, the patient with the religious delusions, were transformed into episodes of ecstasy, while in Laetitia they took more and more the form of attacks of sleep of increasingly prolonged duration. At the age of 20 years she remained almost constantly in bed, with the feeling expressed in her own words, "that every day she took a new step toward total loss of consciousness," and she ended by falling completely asleep, so that one could not awaken her.

In my first communication, I told how I was able to organize the treatment of this patient at the Salpêtrière and watch this strange sleep, which was complete for four years and incomplete the fifth year. In the course of this sleep, by maneuvers resembling hypnotism, I had conversations with the patient for half an hour each week and collected a mass of documents bearing on this singular condition, a state of intellectual activity with doubts and a feeling of unreality in regard to all things—objects, persons and herself—to events of the present and especially of the past. During this great sleep, Laetitia almost every day had major convulsions of hysterical form, which became fewer toward the end of the sleep. However, her organic condition remained almost normal, especially as regards nutrition, which was obviously a difficult matter, and the excreta showed no important anomaly. The organic nervous condition—the various reflexes which I studied continually—has been the object of detailed examination by Dr. A. Souques, without any abnormality being noted.

When sleep seemed to be much diminished, when Laetitia appeared to show in the course of the day an activity which was limited but apparently sufficient, I sent her home to her family, but it was not long before the family was in trouble and complained that they could not look after her on account of new disorders, different from the preceding, to which I wish to draw attention.

Her parents said in jest that to satisfy their daughter they would need to organize in their house a fire brigade to bring her water. The patient, who at the hospital during sleep drank little water, demanded more and more water, in proportion as she took more interest in life. She soon was drinking from 12 to 13 liters of water a day, then 15 liters. There was diminution in the course of severe treatment in the various hospitals for the care of mental disorders in which she was placed, but she could not support the restriction of fluid intake. She became very thin and ill. It was necessary to yield to her, and in the course of years she arrived at the consumption of 30 liters of water a day. In recent years her condition has improved, and at present she is satisfied with 6 and sometimes even with 3 liters of water daily. Naturally, the quantity of urine increased in proportion.

Another symptom which developed after the long sleep and caused many difficulties in the conduct of the patient was a singular disturbance of gait. The patient presents no disorder, no paralysis, of the legs when one examines her in bed or seated on a chair, but she is unable to stand without something to lean on, however

trifling. She can walk a great deal, even rapidly, but on one condition: It is necessary that some one have an arm around her waist and support her a little, or appear to support her. As soon as she ceases to feel the contact of an arm on her back, she collapses suddenly on her knees. She walks quickly and can cover miles when a maid has a hand on her back, but she claims that she cannot take a step if one withdraws the hand. It is curious that she moves about quickly in her room, on all fours on her knees. In the water, for she loves sea-bathing, she swims well without help and says that she is supported by the water.

One must add to these new disorders the old troubles, the hysterical attacks, which have persisted at least partly; they are less frequent and severe than before but appear once or twice a week; after these convulsive attacks she sleeps for several hours.

The peculiar mental condition has persisted; Laetitia is intelligent and interested in many things; she frequently offers rather amusing comments. An interesting detail: She was capable of writing French verse of tolerable quality during the prolonged sleep, but after waking she gave up her poetry.

She presents in the highest degree the characters of psychologic asthenia. She is incapable of continuing an action for any time or of prolonging an effort. She is timid and embarrassed when one looks at her, cannot fix her attention clearly and for some time is preoccupied with a swarm of reveries; she is upset by the least emotion. She always has need of being directed and demands this in an obsessive manner.

The diagnosis of such a condition, which has lasted more than thirty years, is not free from difficulty. The hypothesis which comes most naturally to one's mind, in view of the prolonged sleep and the diabetes insipidus, is that there must be an important cerebral lesion—in particular, a tumor in the region of the hypophysis. This problem has been studied constantly for twenty years; on no occasion has any restriction of the field of vision been observed on either side. No ophthalmologist has observed any modification of the fundus. Repeated roentgenologic examinations have shown no relevant modification of the base of the skull. All treatments with extracts of pituitary have been without result. Finally, this summer I sent the patient to the laboratory of M. de Martel, to whom I spoke of a possible operation. Examination there gave completely normal findings, and no operation was considered possible.

There still remains the task of correlating the symptoms with the incontestable neuropathic condition. The disturbances of behavior and the feelings of unreality are clear expressions of psychologic asthenia. The hysterical convulsions are discharges of energy mobilized without effort, the tension of which the asthenic patient is unable to support. I believe that one must give a similar explanation for the peculiar disorder of gait, which is related to agoraphobia and basophobia.

I am embarrassed by the polyuria; it is extreme for a patient with diabetes insipidus. Can one consider it merely as the result of an obsession for drinking water? Is it merely a potomania due to a special mental state, or must one admit, in addition to the neuropathic condition, a small lesion of obscure nature in the region of the pituitary?

It is on this point that I should be glad to have the opinion of my colleagues.

DISCUSSION

DR. C. M. CAMPBELL: After this dramatic presentation of an unusual case by Professor Janet, he asks with irony that one suggest a solution of his problems. This patient had signs of instability in childhood; at puberty psycholeptic attacks developed, while more ordinary hysterical reactions also appeared. Her recurrent attacks of sleep are intriguing. Why does one person react with vomiting, while others tremble or turn pale or are struck down? Why did Madeleine manifest religious ecstasies and Laetitia sleep? One has to consider environmental influences, the internal dynamics of the personality, the possibility of physiologic anomalies. Is the sleep an attitude, or is it something determined by an impersonal process? The fact that a tumor can be excluded may still leave the possibility of a process

in the region of the hypophysis sufficient to disturb the vegetative centers. But even though there is not some process, might one still postulate a diencephalic sensitiveness, a special physiologic endowment? Or is it really a drama of sleep? The reactions of a hysterical person are dramatic and have a definite relation to the audience. The duration of the drama is unusual in this case. Why do catatonic patients lie for so long in stupor? I would suggest that Professor Janet repeat the procedure of 1921 and in fifteen years give a further report of this case.

DR. W. G. LENNOX: Dr. and Mrs. Gibbs and I have been studying patients with a similar condition by means of electrical potentials generated by the brain. Some of these patients showed electrical activity which we believe is characteristic of epileptic processes. From my point of view, I should look on this case as one of epilepsy combined with narcolepsy and psychosis.

DR. P. YAKOVLEV, Waltham, Mass.: It has been an exceptional pleasure to hear the presentation of the history of a patient who has been observed keenly for so many years and is described so vividly. Not being competent in psychologic matters, I do not dare to make any comments of my own concerning the psychologic problems aroused by this remarkable case. I may confess, however, that were my opinion asked as to the nature of the condition, without my knowing the preeminent competence of the observer, I should regard the history of the patient as being extremely suggestive of epilepsy. The disturbances in the sphere of vegetative life, the instability of autonomic regulation of the steady state of the internal medium, with resulting disturbances in the sphere of the mental life and behavior of the patient are, I believe, the general formula which characterizes epilepsy. The history of Professor Janet's patient would seem to answer this formula; all the symptoms presented by her may be commonly seen in cases of typical epilepsy, although in lesser degrees. On the other hand, I wonder whether there is room for quarrel between a psychologic and a neurologic, or rather a neurobiologic, interpretation of the history and symptoms. If one considers the person not merely from the standpoint of each given moment of his life but as being at each moment the product of all his past; i. e., if one considers his biologic "becoming" as Professor Janet does when he studies the evolution of his patients' lives over so many years, the question of diagnostic label to be applied is somewhat beyond the point. It would seem evident that the neural organization of the person as he proceeds through life and what is called his "psychology" are but two aspects of the process of his biologic "make-up." The psychologic and the neurobiologic problems aroused by Laetitia's life and symptoms can both be placed within the scope of her biologic "make-up."

DR. I. CORIAT: I remember how intrigued I was several years ago with the beautiful histories and the manner of presenting clinical material in Professor Janet's *"Les névroses et idées fixes."* I shall say a few words principally because I disagree with the diagnosis of the discussers, although I have been impressed with this significant work. As I have reconstructed this case in my mind, partly from the abstract and partly from what has been presented tonight, I believe that one is dealing here with a preeminently hysterical neurosis in spite of the epileptiform seizures, which are probably hysterical and not epileptiform. It is significant that Laetitia's difficulty appeared at about puberty, a period at which there is a profound disturbance of the sexual life, possibly with conflicts over the developing sexuality. I think that the predominant symptoms of somnambulism, narcoleptic attacks, prolonged sleep, necessity for spoon feeding and incontinence of urine are representative of a complete break with or flight from reality. The flight in this case seems to be a deep regression, a regression to the earliest years of childhood, in fact, to infancy, a break with adult reality. This state of sleep is to her a world more real than that about her. Of course, one may be permitted to ask the question: What was there in the inner life of the patient which motivated this regression? Some light may be thrown on this difficult problem of the transition from reality to unreality in what she has said to Professor Janet in her restricted life.

PROF. PIERRE JANET: The observations of Dr. Lennox and Dr. Yakovlev strike me as just and important. I have for a long time been accustomed to say

that the epilepsies furnish one with most important data for the study of psychopathology. As Voisin formerly observed, before the fit there is a sort of vital excitation—I should say today, a rise of the psychologic level—which gives an opportunity to study all conditions of elation; after the attack there is considerable lowering of the level, with all forms of depressive states.

I have described a patient of this kind who before the attack presented a true delusional state with elation, who found everything beautiful and admirable, who was loved by all and who loved everybody. After the attack there was, on the contrary, a true depressive delusional condition. But these remarks on epilepsy could be applied to all possible conditions, for always and everywhere one will find these oscillations of psychologic force and tension.

It is certain that the word "hysteria" proposed by Dr. Coriat is a more precise term to apply to a condition of this type. One again has sufficient courage to pronounce this word, which in France has been somewhat tabooed since the disputes between Charcot, Bernheim and Babinski. This diagnosis is necessary in many cases, especially from the point of view of psychopathology, for it denotes a particular form of psychologic asthenia which is characterized especially by the marked narrowing of the field of consciousness.

Taken as a whole, Laetitia presents a severe degree of psychologic asthenia, with symptoms of discharge and narrowing of the field of consciousness, but the difficulty still remains of bringing the curious symptoms of polydipsia, extreme for an organic disorder, and of polyuria into relation with these obvious psychologic disorders.

The comments which have been made this evening will help me to continue this study.

PHILADELPHIA NEUROLOGICAL SOCIETY

Oct. 23, 1936

F. H. LEAVITT, M.D., *President, in the Chair*

PALATAL-PHARYNGEAL-LABIAL MYOCLONUS: REPORT OF A CASE. DR. E. MARCOVITZ and DR. B. J. ALPERS.

D. J., a Negro aged 32, who was admitted on Aug. 17, 1936, to the Philadelphia General Hospital, under the care of Dr. B. J. Alpers, complained of gradual progression of staggering gait and weakness of the legs for three years. During the last year he had experienced diplopia, which had increased in frequency. He had had mumps at the age of 17 years. In 1925, at the age of 21, he was in the Philadelphia General Hospital, where a diagnosis of typhoid was made. In 1927 he was readmitted to the hospital, with a history of pains in the head and neck. He had diplopia and drowsiness, both of which disappeared. The course was afebrile. Gait was unsteady. The spinal fluid contained 210 polymorphonuclear leukocytes. A diagnosis of encephalitis was made, and the patient was discharged as improved. Since that time he has received treatment for syphilis in the outpatient department.

Examination.—There were: a slow, careful gait, with a slight tendency to stagger to the left; marked swaying in walking heel to toe, but no falling, and inability to stand on either foot alone. There was dysynergia in both arms. Motor power was good in the upper extremities but definitely impaired in the distal lower portions of the lower extremities, especially on the left. The deep tendon reflexes in the upper extremities were equal and active, as were the abdominal reflexes. The left patellar jerk was diminished; the right was more active and was elicitable with reenforcement. The right achilles jerk was also diminished. There was no clonus or Babinski response. Heel to knee tests showed mild ataxia with

the eyes open or shut. Finger to nose tests were performed slowly, but without ataxia. The touch, pain, vibration and position senses were normal.

The pupils were small, equal and irregular and reacted well in accommodation. The right pupil did not react to light, while the left reacted slightly. There was ptosis of both eyelids, much more on the left. There were slight paresis of both external rectus muscles and impairment of convergence on the left. Irregular, inconstant nystagmoid movements were present on lateral gaze to either side. The corneal reflexes were decreased. There was questionable weakness of the lower part of the face on the right, but no weakness of the palate or tongue. There was no impairment of hearing. Phonation had a palatal quality.

Special Features.—The outstanding feature in this case was the synchronous movement of the right side of the lower lip, the palate and the pharyngeal fauces, and probably of the larynx. The lower lip moved constantly, synchronously with the palate, and involved chiefly the right side, but to a certain degree the left. There was a slight movement of the upper lip at times. There was a vertical movement of the soft palate, the fast component being upward. This was at the rate of 120 per minute. The pharyngeal wall moved with it, and a synchronous movement of the cricoid cartilage could be seen. Contraction of the muscles. The movements of the palate were not completely regular.

These movements apparently were not felt by the patient and did not cause him discomfort.

Laboratory Data.—The urea nitrogen and sugar contents of the blood were normal. The Wassermann reaction of the spinal fluid was negative. The roentgenogram of the skull revealed nothing abnormal.

Comment.—We present this case as one of palatal-pharyngeal-laryngeal-labial myoclonus. The etiology is still undetermined but seems to rest between encephalitis and syphilitic cerebral vascular disease, with the essential lesions involving the central tegmental tract in the brain stem. Encephalitis is the more likely etiologic factor.

DISCUSSION

DR. B. J. ALPERS: This case is presented mainly to demonstrate the myoclonus. While there was no movement of the vocal cords, there was definite contraction of the small muscles, which one could feel in the region of the cricoid cartilage. These were synchronous with the movements of the palate. The movements of the lip were also synchronous with the movements of the palate. We have no specific ideas as to the etiology, but there was a definite suggestion of encephalitis a few years ago.

DR. D. J. MCCARTHY: Has there been a definite attempt at localization of the lesion?

DR. B. J. ALPERS: I cannot speak from personal experience in cases of this condition, but in the literature hypertrophy of the inferior olive and degeneration of the central tegmental tract have been mentioned in most cases. In some instances there has been also degeneration of the opposite dentate nucleus. I cannot say what is the relation of these structures to the myoclonus.

DR. PAUL SLOANE: I know that the condition has been termed "myoclonus," but it seems to me that the movements resemble rather those of parkinsonism, since they are coarse and rhythmic and tend to cease on voluntary innervation. In many cases reported lesions have been present also in the basal ganglia.

DR. M. A. ORNSTEEN: The cases I have seen were all those of encephalitis.

DR. E. SPIEGEL: I saw a number of patients with encephalitis who had clonus of the lower jaw, synchronous with clonus of the tongue. Enormous salivation was another feature in these cases. Klein observed clonus of the velum palatinum in association with lesions of the dentate nucleus of the cerebellum.

DR. B. J. ALPERS: True myoclonus is rarely due to epidemic encephalitis, but to multiple sclerosis, tumor or vascular disease. In the case reported by Gabrielle Lévy the condition was said to be due to encephalitis, and in a case of

Riley's it appeared to be encephalitic. However, encephalitis is by no means the most common cause; it rarely produces true rhythmic palatal myoclonus.

ISOLATED BILATERAL PARALYSIS OF THE ABDUCENS NERVE: REPORT OF TWO CASES. DR. J. C. YASKIN, DR. F. H. LEAVITT and DR. R. DENISON (by invitation).

Bilateral involvement of the abducens nerve is occasionally observed in the following conditions:

1. Intramedullary lesion, when there is associated implication of the seventh nerve and of the long sensory and motor pathways. The etiologic factor in these cases is neoplastic or inflammatory, as in a recent case of disseminated encephalitis observed by one of us (J. C. Y.). The onset in these conditions is usually gradual.

2. Syphilitic basal meningitis. Uhthoff (quoted by Nonne, Max: Syphilis and the Nervous System, translated by C. R. Ball, Philadelphia, B. Lippincott Co., 1913, p. 135) stated that in 150 cases of neurosyphilis paralysis of the abducens nerve occurred 27 times and bilateral paralysis of the abducens nerve 6 times. Bilateral paralysis of the abducens nerve of syphilitic origin has been reported by G. H. Roger (*Rev. d'oto-neuro-opht.* **10**:520 [July-Aug.] 1932).

3. Barbiturate intoxication, as reported by Palmer (*New Zealand M. J.* **35**:21 [Feb.] 1936), and in association with diabetes, as reported by Villard, Viallefont and Bouzigues (*Rev. d'oto-neuro-opht.* **12**:425 [June] 1934).

4. Increased intracranial pressure as a late symptom of tumor of the brain (reviewed by Spiller, W. G.: *Ann. Surg.* **101**:329, 1935).

5. Facial diplegia, with which it has been reported to be associated as a congenital form by a number of authors: a congenital disease characterized by bilateral clubfoot, facial palsy and paralysis of the abducens nerve (Alajouanine, T.; Huc, G., and Gopcevitch, M.: *Rev. neurol.* **2**:501 [Nov.] 1930); a congenital syndrome characterized by bilateral facial paralysis, paralysis of the abducens nerve and clubfoot (Decourt, J., and Perreau, P.: *Arch. de méd. d. enf.* **38**:419 [July] 1935); congenital bilateral paralysis of the abducens nerve (Phillips, W. H.; Dirion, J. K., and Graves, G. O.: Congenital Bilateral Palsy of the Abducens, *Arch. Ophth.* **8**:355 [Sept.] 1932); bilateral paralysis of the abducens nerve and exophthalmos (Roger, H.; Aubaret, and Reboul-Lachaux, J.: *Rev. d'oto-neuro-ocul.* **5**:36 [Jan.] 1927); congenital bilateral paralysis of the facial and oculomotor nerves and bilateral clubfoot (Gareiso, A., and Barbieri, C. A.: *Prensa méd. argent.* **20**:1713 [Aug. 2] 1933).

6. Lymphatic leukemia (Howell, A., and Gough, J.: *Lancet* **1**:723 [April 2] 1932).

7. The bilateral Gradenigo syndrome (Malan, A.: *Ann. d'oto-laryng.*, February 1931, p. 129) and sinus thrombophlebitis (Greenfield, S. D.: Etiology and Pathology of Paralysis of the Abducens Nerve Associated with Sinus Thrombophlebitis, *Arch. Otolaryng.* **19**:336 [March] 1934).

8. Cranial trauma (Loepp, W.: Röntgenbefund bei traumatischer Abduzenslähmung, *Röntgenpraxis* **7**:325 [May] 1935; Dupuy-Dutemps, P.: Paralysie traumatique des deux nerfs de la sixième paire, *Bull. et mém. Soc. franç. d'opht.* **48**:444, 1935; Rollet, J.: Pathogénie de la paralysie bilaterale du nerf moteur oculaire externe, *Bull Soc. d'ophth. de Paris*, January 1933, p. 65; Névrotomie opticociliaire: Résultats éloignés, *Lyon méd.* **141**:563 [May 13] 1928).

Review of the literature reveals that bilateral palsy of the abducens nerve is usually of gradual onset and is frequently accompanied by other signs of focal lesions in the brain. The observation of 2 patients in whom the onset of the palsy was rapid and limited to the abducens nerve prompted the following report:

CASE 1.—H. D. W., a woman aged 51, a widow, was admitted to the Graduate Hospital of the University of Pennsylvania on March 12, 1936, and was discharged on April 2. The family and the past medical history were irrelevant except that several members on the paternal side had deafness and the patient had been deaf

since late adolescence. In addition, the patient had had appendectomy, tonsillectomy and thyroidectomy. On Jan. 22, 1936, the car which she was driving skidded into a pole. She did not remember exactly what happened, but evidently she struck her face against the steering wheel. When she regained consciousness, she had a tooth and part of the steering wheel in her hands. If she was unconscious at all it was only for a short time. On arriving at the hospital she had fracture of the maxilla, loss of three teeth and complete internal convergence strabismus. A roentgenogram of the skull failed to reveal any fracture other than that of the maxilla. The spinal fluid was not under increased pressure; it was clear and normal in every detail.

Examination at the Graduate Hospital revealed no significant abnormalities except complete bilateral paralysis of the external rectus muscle and nearly complete bilateral deafness. A second roentgen examination failed to reveal evidence of fracture of the skull. All other laboratory tests gave normal results.

The patient did not improve during her residence in the hospital and when last examined still had complete bilateral paralysis of the abducens nerve.

CASE 2.—D. W. P., aged 58, single, a tinsmith, was admitted to the Philadelphia Orthopaedic Hospital and Infirmary for Nervous Diseases on March 21, 1936, complaining of headache, stiffness of the neck and turning inward of the eyes. The family and the past medical history were irrelevant. On March 5 he awoke with rigidity of the neck and pain in the head. On March 7 both eyes turned inward, and he had persistent diplopia. He made no other significant complaints. The patient was well nourished, with normal pulse and temperature; the blood pressure was 178 systolic and 106 diastolic; there were an apical systolic murmur and moderate arteriosclerosis. The mental condition was clear. Neurologic abnormalities included moderate angiosclerosis of the retinal vessels, complete bilateral paralysis of the external rectus muscles and moderate rigidity of the neck, without the Kernig or the Brudzinski sign.

Lumbar puncture revealed low pressure of the spinal fluid, which was xanthochromic and thick. It was necessary to perform aspiration in order to obtain a specimen. The spinal fluid contained 44 erythrocytes and 152 mg. of protein per hundred cubic centimeters; the Pandy reaction was plus 4, and the colloidal gold curve, 0121111000; Fehling's solution was reduced, and the Wassermann reaction was negative. The Wassermann reaction of the blood was also negative. Roentgen examination of the skull revealed a rather elongated and deep sella turcica, measuring 1.8 by 1.2 cm. in depth; there was no evidence of erosion or of increased intracranial pressure.

The patient's condition gradually improved; the blood pressure dropped, so that on May 9 it was 136 systolic and 86 diastolic. Examination of the spinal fluid on April 7 showed 12 cells, a total protein content of 57 mg. per hundred cubic centimeters and a colloidal gold curve of 0011111000. On May 4 there was nearly full rotation of the left eye but some weakness of the right external rectus muscle. When the patient was last examined, on September 15, there was complete recovery of both external rectus muscles.

Comment.—In consideration of the origin, cause and relationship of the abducens nerve, the sudden and isolated bilateral involvement of the nerve in these cases can best be explained by assuming that the lesion was in Dorello's canal. It is difficult to conceive of a bilateral lesion within the pons, the cerebellopontile angle or the cavernous sinus which is not associated with many other symptoms. In Dorello's canal the abducens nerve is nearly isolated and can be involved without implicating any other structures. Furthermore, the structure of Dorello's canal is such that it can easily implicate the abducens nerve. The researches of Eagleton (Localized Bulbar Cisterna (Pontile) Meningitis, Facial Pain and Sixth Nerve Paralysis and Their Relation to Caries of the Petrous Apex, *Arch. Surg.* **20**:386 [March] 1930) and ohters (Dorello: Ueber de Ursache der transitorischen Abduzenslähmung bei Mittelohreiterungen, *Internat. Zentralbl. f. Ohrenh.* **4**:418, 1906; Vail, H. H.: Anatomical Studies of Dorello's Canal, *Laryngoscope* **32**:569, 1922; Wheeler, J. M.: Paralysis of the Sixth Cranial Nerve Associated with

Otitis Media, *J. A. M. A.* **11**:1718 [Nov. 23] 1918, and Sjöberg, A. A.: Contribution to Knowledge of the Genesis of Certain Symptoms of Apicitis, *Acta otolaryng.* **19**:479, 1934) have shown that this canal is frequently anomalous and, when unusually narrow or short, may be the cause of paralysis of the abducens nerve. In case 1 the impact to the maxilla may have caused concussion, resulting in immediate compression of the two nerves. In case 2 the subarachnoid hemorrhage may have caused sufficient secondary meningitis to produce bilateral compression of the nerve within this canal. It is interesting that of the numerous cases of spontaneous subarachnoid hemorrhage this is the first in which there was isolated bilateral paralysis of the sixth nerve.

DISCUSSION

DR. F. H. LEAVITT: The second patient presented by Dr. Yaskin was under my care at the Orthopaedic Hospital. He has returned to work and has normal muscular action of both external rectus muscles. I consider him entirely cured. It was an interesting observation that a flat plate of the skull showed visualization of the artery and the circle of Willis and that there was marked evidence of calcifying arteries elsewhere in the body. The impression was that the patient had had a hemorrhage from one of these sclerotic vessels. Whereas the Wassermann reaction was negative, the patient consumed large quantities of potassium iodide, without toxic effect; with this treatment, or in spite of it, he recovered.

DR. R. A. GROFF: Dr. Yaskin has explained the cause of the bilateral palsy of the sixth nerve adequately. In cases of tumor of the brain I have seen marked grooving of the sixth nerve by the anterior cerebellar artery. Some of the patients showed no clinical evidence of this pressure. However, it is conceivable that after a certain length of time the nerve may suddenly give out. This may be another explanation for paralysis of the abducens nerve in the case of arteriosclerosis described, in which it is possible that the thickened vessels made pressure on the nerve.

DR. HELENA E. RIGGS: Last year, during a rather severe epidemic of meningococcic meningitis, several cases of bilateral palsy of the sixth nerve associated with increased intracranial pressure occurred at the Philadelphia General Hospital. When I had charge of the nurses at the Philadelphia General Hospital, a nurse with isolated unilateral palsy of the sixth nerve recovered within thirty-six hours after administration of diphtheria antitoxin. This nerve lies against the bone, with the weight of the brain pressing against it, which may account for the frequency with which it is involved in cases of increased intracranial pressure accompanying numerous intracranial conditions. Dr. Yaskin's second case may have been one of subarachnoid hemorrhage, with the general increase of intracranial pressure which is associated with such a condition.

DR. J. C. YASKIN: Within the last six weeks I have seen a patient with bilateral palsy of the sixth and seventh nerves associated with marked increase in intracranial pressure. He had a large abscess in the right frontal lobe. The capsule was so thick that it could be shelled out with the fingers. When the lesion was removed, the patient recovered completely, with disappearance of the paralysis of the nerves.

SPINA BIFIDA TREATED BY MULTIPLE TAPPINGS. DR. G. M. DORRANCE (by invitation).

I am again presenting the white child, P. R. O., aged 4 years, with spina bifida who was shown before this society when she was 2 years old. The patient was treated by multiple tappings. When the child was first admitted to the hospital, at the age of 3 months, she had a cystic mass in the lower lumbar region, with considerable bulging of the anterior fontanel. No operative procedure has been attempted. The patient was tapped sixteen times between Nov. 12, 1932, and June 5, 1933; the amount of fluid withdrawn varied from 50 to 84 cc. Tapping was performed by inserting a spinal needle into the skin at a point 1 inch

(2.54 cm.) from the border of the sac. Evidence of increased pressure was indicated by bulging of the fontanel. The child reacted well, however, but on one occasion the surface of the sac became infected, and necrosis of the superficial part occurred. No evidence of meningeal irritation took place, and the ulceration eventually healed. On July 11, 1933, tapping was again done, but no fluid was obtained; no more aspirations were attempted, as there was no further indication for this procedure. The child has at no time showed signs of hydrocephalus. In January 1934 she appeared to have shortening of the left tendo achillis and was referred to an orthopedist for treatment; she is now wearing an appliance.

The slides show the improvement in the child's condition. Roentgen examination of the skull revealed no evidence of hydrocephalus, although the anterior fontanel showed retarded closing. The child's mentality does not seem to be impaired at present, nor has it been heretofore. In view of the fact that operative procedure has proved so unsatisfactory and the mortality rate from it so high, with hydrocephalus in a large percentage of cases and paralysis of the rectal and vesical sphincters after operation, I believe that treatment by multiple tappings is a conservative way of handling certain of these cases.

DISCUSSION

DR. A. M. ORNSTEEN: I notice that the child's forehead is prominent. Has there been any disproportionate increase? Are the characteristics of the configuration of her skull in proportion to those of earlier years? Has the skull enlarged in proportion or in disproportion to her age?

DR. G. M. DORRANCE: The patient had rather a prominent forehead in the first place. Roentgen pictures do not show any evidence of abnormal enlargement. The fontanel is closing but has not yet closed. It might lead one to suspect hydrocephalus.

DR. R. A. GROFF: Dr. Dorrance has presented a unique way of handling meningocele and meningomyelocele in its early stages. From the appearance of the sac in his patient, I should call it a meningomyelocele, since there is evidence of damage to the roots. In some cases difficulty may arise in that the sac is loculated, necessitating several tappings in order to evacuate the sac. Operative results are not brilliant, but I disagree with Dr. Dorrance in saying that in all cases in which operation is performed hydrocephalus develops. Excellent results have been obtained by following the method of Penfield in dissecting out the sac and invaginating it. One value of the treatment demonstrated by Dr. Dorrance is that the sac may thus be prepared for operation when the covering is raw and in danger of rupture.

DR. G. M. DORRANCE: I did not mean to convey the impression that in all cases in which operation is performed hydrocephalus develops. I said, or meant to say, that it does in most instances. I have seen 3 patients who had paralysis of the rectum after operation. My feeling is that if I could keep other patients carrying on as well as this child, I should let them all go until they are older, but this case is the only one in which the treatment was successful. In 2 other cases hydrocephalus developed. I do not know how to judge this treatment, but this child has done well. If hydrocephalus is going to develop, why should she be submitted to an operative procedure early in life? If she can live to 8 or 9 years of age and then undergo an operation, I think she would have a better chance.

NEUROLOGIC ASPECTS OF PETROSITIS. DR. J. C. YASKIN AND DR. KARL KORNBLUM (by invitation).

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DISCUSSION

DR. MATTHEW S. ERSNER: Dr. Yaskin emphasizes that petrositis should not be considered from an etiologic aspect alone, as the disease presents many interesting neurologic manifestations and the otologist invariably seeks counsel when such complications arise. Petrositis is a distinct clinical entity based on an

anatomic and pathologic background; it is the result of inflammation and infection of the petrous portion of the temporal bone. The clinical manifestations depend on the type of the temporal bone involved.

There are three types of temporal bone: (1) pneumatic, (2) diploic and (3) sclerotic and a combination of these varieties. When the pneumatic petrosa becomes infected, empyema or osteitis results. Should a diploic petron become involved, osteomyelitis takes place. In a completely sclerotic temporal bone, petrositis cannot occur, for this type of bone lacks the elements (air cells and bone marrow) necessary for this disease.

Anatomically, the temporal bone occupies a unique and strategic position in its relationship to the cranial nerves, carotid artery, lateral sinus, bulb of the jugular vein and middle and posterior cranial fossae. All the cranial nerves, except the first and second, bear a close relationship to the temporal bone. Therefore, one can readily understand why so many neurologic phenomena in the form of palsy or pain occur.

Pain, the outstanding symptom, is deep in the eye and is due primarily to involvement of the gasserian ganglion and secondarily to pressure on the ophthalmic branch of the fifth nerve. The other symptoms in order of importance are: vertigo, occasional facial palsy and, of least importance, palsy of the external rectus muscle.

The so-called Gradenigo syndrome, consisting of pain referred to the fifth nerve, suppurative otitis media and palsy of the external rectus muscle, bears little relationship to petrositis. These symptoms are merely a syndrome which cannot be explained rationally from an anatomic and a pathologic standpoint, although one may conceive that Dorello's canal may be partly responsible for the palsy of the sixth nerve.

The petrosa may become infected by continuity, contiguity or retrograde thrombosis. Infections resulting from continuity and contiguity lend themselves to surgical treatment, while the retrograde thrombotic variety always terminates in disaster.

The surgical approach depends on the location of the infection. Eagleton unlocks the petrous pyramid and saves the structure of the middle ear, thus preserving hearing. The other classic procedure is radical mastoidectomy, with exenteration of all the cells and a thorough search for fistulous tracts. These tracts may be perilabyrinthine, supralabyrinthine, infralabyrinthine or peritubal.

With a small curet or an electric drill, one can readily enter the petrosa through the middle ear and thus induce drainage. Another procedure is to remove the tegmen tympani and follow the petrosa forward, inward and downward to the petrous apex.

In conclusion: (1) petrositis may be secondary to mastoiditis; (2) petrositis may be secondary to otitis media; (3) petrositis due to retrograde thrombosis does not respond to surgical or other treatment; (4) roentgen manifestations of petrositis without clinical symptoms should be watched carefully, and no surgical intervention is indicated; (5) roentgenographic studies of the mastoid should include key plates of the petrosa; (6) the surgical approach is simple, indispensable and life saving; (7) spinal drainage is indicated when there is increased intracranial pressure and when meningeal symptoms are present, and (8) sometimes complete simple mastoidectomy will open up avenues for drainage and thus avert more radical surgical procedure on the petron.

DR. E. SPIEGEL: Dr. Yaskin gave a complete description of the anatomic picture and the differential diagnosis. I wish to mention one point only, i. e., the relation of the postganglionic papillodilator fibers to the carotid canal in the petrous bone and to the medial wall of the cavum tympani. It is known from experimentation on animals that if one opens the middle ear and removes the mucosa of the medial surface of the tympanum, the pupil becomes myotic. In studying this problem in Dr. Alexander's clinic in Vienna, I found in some patients with otitis media symptoms of involvement of the pupil. There seems to be some variation in the anatomic relation of the pupillodilator fibers to the wall

of the cavum tympani, since only some patients with otitis media have symptoms of paralysis of these fibers. If infection progresses from the tympanum into the carotid canal, one would expect more frequent involvement of the postganglionic fibers from the upper cervical ganglion. The result of involvement of these fibers is not necessarily myosis, for if one extirpates the upper cervical ganglion there develops after a few weeks paradoxical dilatation of the pupils, due to development of hyperexcitability of the dilator muscle on which blood stimuli (e. g., epinephrine) act. One can recognize this hyperexcitability of the dilator muscle in a simple way. If one instills a 1: 10,000 dilution of epinephrine hydrochloride into the conjunctival sac on both sides, there develops more marked dilation of the pupil on the diseased side. When the infection progresses toward the petrous bone, study of these reactions of the pupil may be of help.

DR. J. C. YASKIN: I wish to thank Dr. Ersner and Dr. Spiegel for their discussion. I did not think of the sympathetic nervous system as connected with this condition. I have never seen a frank Horner's syndrome in connection with disease of the mastoid. When infection invades the carotid canal, it is usually fatal. It is a point well taken and one which I shall look for in the future.

INTRINSIC REGULATION OF THE CEREBRAL CIRCULATION. DR. CARL F. SCHMIDT (by invitation).

Changes in the blood flow in various parts of the brain of anesthetized (or decerebrated) curarized cats were detected by means of a small, artificially cooled thermocouple introduced directly into the tissue. Studies have been made in the medulla (Schmidt, C. F., and Pierson, J. C.: The Intrinsic Regulation of the Blood Vessels of the Medulla Oblongata, *Am. J. Physiol.* **108**:241 [April] 1934), the hypothalamus (Schmidt, C. F.: The Intrinsic Regulation of the Circulation in the Hypothalamus of the Cat, *Am. J. Physiol.* **110**:137 [Nov.] 1934) and the parietal region (Schmidt, C. F.: The Intrinsic Regulation of the Circulation in the Parietal Cortex of the Cat, *Am. J. Physiol.* **114**:572 [Feb.] 1936), and similar observations in the occipital lobe are now under way. Vasomotor (constrictor) innervation via the cervical portion of the sympathetic chain appears to be absent in the medulla, only occasionally and weakly present in the occipital region (external and mesial surfaces), fairly constant in the hypothalamus and most constant and most highly developed (of the regions so far studied) in the parietal region. The response of the cortical circulation to electrical stimulation of the sympathetic nerves differs from that of extracranial areas (muscle, kidney and spleen) in the presence of a latent period, slow progression of the effect and slow recovery; these differences suggest that the cortical effect is due to a humoral mechanism. No evidence of an intrinsic cerebral vasomotor nervous system was observed; chemical agents (asphyxia, anoxemia and excess of carbon dioxide) and electrical stimuli (faradization of the central nerve axis) were used; any effects on the cerebral blood flow were always in the direction of an increase. No evidence of vasodilator nerves to the cerebral vessels was found; the vagodepressor and carotid sinus nerves were tested. Chemical agents, however, had consistent effects: Carbon dioxide excess produced marked increase in the blood flow in all regions tested, and carbon dioxide deficiency, a comparable decrease; lack of oxygen also increased the flow, but its maximal effect was significantly less than that of carbon dioxide; oxygen excess reduced the flow most markedly in the mesial surface of the occipital lobe and in the parietal region. Anesthetics (ether, chloralose, barbiturates and ethyl carbamate) increased the blood flow, presumably because of dilation of the cerebral vessels. Epinephrine had a weak and probably negligible constrictor effect in the hypothalamic region and none at all in the other areas studied. Solution of posterior pituitary only increased the flow in all cases. Choline derivatives (acetylcholine, acetylbetamethylcholine and ethyl ester of betamethylcholine) produced marked increase in the blood flow in all the regions of the brain investigated; glyceryl trinitrate and amyl nitrite acted similarly, but much less markedly.

At the present stage of these investigations, it seems probable that there is an intrinsic control of the cerebral circulation in the anesthetized (or decerebrated) curarized cat but that it differs from the intrinsic control of most other vascular areas in that the regulation is accomplished by chemical factors (specifically carbon dioxide) rather than by nervous factors and that it is achieved by varying degrees of dilation of vessels which have a high intrinsic tone and go into spasm when the tone is not antagonized by chemical vasodilator agents, rather than by varying degrees of constriction, through vasomotor nerve impulses, of vessels which owe their tone to such impulses. To what extent this may be true of animals other than the cat prepared as for these experiments it is impossible to say. There is evidence that the cerebral vessels of man go into spasm when the carbon dioxide tension of the blood is reduced by violent hyperpnea, for certain subjects can thus produce unconsciousness in themselves, but not if they have been given a vasodilator drug, such as glyceryl trinitrate. In some cases of the Cheyne-Stokes type of breathing, vasodilator substances (glyceryl trinitrate and choline derivatives) have been found to make breathing regular and to restore consciousness, but the cause of the angiospasm thus indicated remains undetermined. In recent experiments on the occipital cortex of the cat, the blood flow was altered in some cases by illumination of the contralateral eye, but the change may be either an increase or a decrease in blood flow; the circumstances responsible for this variability have not yet been discovered. These preliminary observations are cited as indicating that changes in physiologic activity of a part of the brain are associated with changes in the local circulation, and at present the latter appear to be due to chemical rather than to nervous agencies. Further investigation is under way.

DISCUSSION

DR. B. J. ALPERS: I wish personally to express my appreciation to Dr. Schmidt for this interesting presentation. I had been much interested in the question of cerebral spasm from the clinical standpoint. My enthusiasm has been dampened by Dr. Cobb, however, who says that while spasm of cerebral vessels occurs, it is not sufficient to cause clinical changes, for the degree of impairment of blood flow is not great enough to cause disturbance of cerebral function.

Despite this assertion, I believe that there are clinical phenomena which are explainable only on the basis of cerebral vascular spasm, with resulting hypoxemia or anoxemia. Such are transient hemiplegia, aphasia, and hemianopia, as well as other less striking cerebral manifestations, such as paresthesia. Here the clinic leads the laboratory in its observations. A slight degree of spasm, for example, may be sufficient to produce complete closure of the lumen in a diseased vessel.

The criterion of the situation lies in the length of time to which the tissue is subjected to impaired circulation. No one knows exactly how long cerebral tissue can be subjected to loss or decrease of blood supply without causing the irreversible changes in the cortical cells. Can Dr. Schmidt give any information on this, to me, crucial point?

DR. F. H. LEWY: I was interested to see in one of Dr. Schmidt's charts that with administration of choline an initial increase of blood flow was followed by a secondary decrease. Ten years ago I studied the reaction of the cerebral blood vessels to different drugs with the help of the Trendelenburg drop method. In these experiments injection of choline was followed by a periodic increase and decrease in blood flow. I wish to ask Dr. Schmidt whether he has observed a similar fluctuation.

DR. E. SPIEGEL: I wish to compliment Dr. Schmidt on his interesting results and particularly his improvements in technic. It may be of interest that Obersteiner was first to assume the existence of a vasomotor control of the cerebral vessels. He made this assumption purely on anatomic grounds, based on impregnation methods. I believe that some of the first experiments proving the correctness of Obersteiner's assumption were those of Gaertner and Wagner von Jauregg. They showed that the outflow from the veins of the brain was definitely changed by stimulation of the cervical portion of the sympathetic trunk. Weber, measuring

blood pressure by Huerthle's method in the central and the peripheral stump of the carotid artery assumed that there may be a special vasomotor center for the brain, lying cranial to the rhombencephalic vasomotor center for the whole body. I wish to ask Dr. Schmidt whether his experiments corroborate such an assumption.

In regard to the remark by Dr. Alpers as to the effect of anemia on the nerve cells: I shall mention experiments which Dr. Spiegel-Adolf and I carried out. We studied the effect of anemia by measuring the electrical conductivity with currents of high and low frequencies; the difference in conductivity that normally exists between these currents is diminished in anemia of the brain, indicating impairment of the semipermeable surface films of the cells.

DR. C. F. SCHMIDT: In regard to Dr. Alpers' question: That touches on something which has interested Dr. H. N. Bronk and me. One of the fundamental problems involved is the effect of alterations in blood supply on activity of the nerve cells. Some say that effects of stimulation are due entirely to reflexes and that the direct effect of lack of oxygen or anemia on the nerve cell is purely depressant. We should like to know the answer. As far as the amount of anemia that the cell will stand is concerned, I have nothing but hazy observations, which have been made better by others, to indicate that anemia of a certain duration will lead to irreparable damage. Anemia for even twenty seconds or so is likely to produce definite damage of cerebral functions. The cells of the medulla appear to be somewhat more resistant. With regard to Dr. Lewy's question about the action of acetylcholine: The diphasic nature of the curve was probably due to the fact that the drug was injected intravenously; the first effect was a fall in blood pressure, and cerebral blood flow was decreased accordingly. Subsequently, as the drug was again in circulation, the cerebral vessels become dilated, and the blood flow increased as systemic pressure recovered. In the other cases we gave the drugs by intracarotid injection, and that shows, I think, that the effect on the cerebral vessels is purely a dilator action.

Dr. Spiegel's remarks have interested me a great deal. Dr. Bronk and I tried, in connection with our experiments, to pick up evidence of an intrinsic cerebral vasomotor nervous system. In each level of the brain we investigated, we tried vasomotor stimulation by asphyxia, anoxemia and excess carbon dioxide. These did nothing but increase the blood flow in all parts of the brain. We also tried stimulating the central nerve axis between electrodes in the hope of activating a vasomotor nerve mechanism, but this did nothing unless the stimulus was strong enough to raise the blood pressure; the response was passive. We have used only the two types of stimuli to vasomotor mechanisms, namely, chemical agents and the faradic induction current. If there are intrinsic vasomotor nerve mechanisms in the brain, they evidently do not respond to these stimuli. There is a considerable mass of literature on this subject which is invalid when searched a little more critically. Findings that were made on dogs by various observers are made equivocal by the fact that the dog's external carotid artery is much more important as a source of blood to the brain than the internal carotid artery. In the dog there is a communication between the ophthalmic branch of the internal maxillary artery and the internal carotid artery, and this is often much larger than the internal carotid artery itself. It may be a veritable rete mirabile, and it is inaccessible to occlusion in the living animal. We tried to secure an idea of how much it amounted to and found that while clamping both internal carotid arteries in the dog had no measurable effect on the venous outflow from the brain, clamping the external carotid arteries reduced it 50 per cent. Measured changes in the flow in the internal carotid artery are impossible to localize in a dog or cat. An indicated change may have occurred in the area of the external carotid artery and not in that of the internal carotid artery or the cerebral circulation proper, or the change may have been in the same direction in both the extracranial and the intracranial area, or a change in one may have overshadowed an opposite change in the other. One cannot deduce anything about cerebral vasomotor mechanisms from such observations.

Book Reviews

The Psychobiology of Language. By George Kindsley Zipf. Price, $3.50 Pp. 336, no illustrations. Boston: Houghton Mifflin Company, 1935.

This book, which on the surface bears no relation to clinical psychiatry, is nevertheless of psychiatric interest. Language is behavior and, in application and evolution, is "impelled" and "directed" by trends and laws unknown to the speaker. The observable phenomena of speech lend themselves to the statistical treatment which reveals the trends and laws which maintain the equilibrium of speech and render it an orderly total.

The author studied the phonetic systems of historically related and unrelated languages—modern English and modern German, modern and ancient Chinese, ancient Latin texts, etc.—and his results are striking. One and the same set of laws pervades all the disparate language structures. They are all built on essentially the same phonetic plan. The absolute and relative numbers of "aspirated stops," "unaspirated stops," "voiceless lenes" and "voiceless fortes" are practically the same in all parts of the globe and in all ages. The morphologic structure of language is here revealed as transcending all boundaries of racial and geographic organization in exactly the same manner as do physiology, anatomy, primitive logic, memory and emotionality. Environmental factors play their proper part, but constitutional forces are obviously the main determinants.

The book contains much technical material, but the presentation is so plain and lucid that the informed layman can easily orient himself. The chief lessons to be learned by the clinical psychobiologist are: (1) that by analyzing the observable phenomena of behavior valid generalizing laws can be deduced and (2) that by studying the laws of language much valuable information can be gained with regard to "total behavior" in general. The clinical psychiatrist will find the discussions on parts, totals, equilibrium and their interrelationship both instructive and stimulating.

Dystrophia musculorum progressiva: Eine erblichkeitsmedizinische und klinische Studie. By Bertil Sjövall. Acta psychiat. et neurol., supp. X. Pp. 240. Copenhagen, Denmark: Levin & Munksgaard, 1936.

The material of this book is based on 100 subjects, coming from 100 families. Of the 61 patients in a secondary series who were found in addition to the subjects in these families, 49 were related to the subjects in a horizontal line (most of them brothers and sisters) and only 12 in the vertical line.

Sjövall concludes that the hereditary conditions, as found, correspond best to a dimer-recessive type of inheritance, probably with a pair of factors in the sex chromosome, since somewhat more males have the disease, but he believes that this incidence may be due in part to selection of the material.

For any practical prevention of progressive muscular dystrophy by sterilization these results are not encouraging. In 100 families only 7 parents of diseased persons suffered from this disease; in only 2 of these persons had this been ascertained by medical examination. Ninety-two parents of diseased subjects who had been examined by Sjövall himself were found to be healthy and to exhibit no recognizable signs that would distinguish them from the general population. This book is chiefly of interest for students of heredity and has little practical value for most neurologists.